

Carotid Atherosclerosis and Cognitive Impairment in Nonstroke Patients

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Abstract

Objective: As a vascular risk factor, carotid atherosclerosis is crucial to cognitive impairment. While carotid intima-media thickness, carotid artery plaque, and carotid stenosis can reflect carotid atherosclerosis in different stages, this review aimed to explore researches on the role of carotid intima-media thickness, carotid artery plaque, and carotid stenosis in the progress of cognitive impairment in nonstroke patients and tried to illustrate the possible mechanisms.

Data Sources: We searched the PubMed database for recently published research articles up to July 2017, with the key words of “carotid atherosclerosis,” “carotid intima-media thickness,” “carotid plaque,” “carotid stenosis,” “nonstroke,” and “cognitive impairment.”

Study Selection: Articles were obtained and reviewed to analyze the role of carotid atherosclerosis such as carotid intima-thickness, carotid plaque, and carotid stenosis in the progress of cognitive impairment in nonstroke patients and the possible mechanisms.

Results: In recent years, most studies proved that by evaluating carotid atherosclerosis with ultrasonography, carotid atherosclerosis accounts for the development of cognitive decline in nonstroke patients. Carotid atherosclerosis not only impairs the subtle general cognitive function but also decreases the specific domains of cognitive function, such as memory, motor function, visual perception, attention, and executive function. But, it is still controversial. The possible mechanisms of cognitive impairment in nonstroke patients with carotid atherosclerosis can be classified as systemic global cerebrovascular function, small-vessel diseases, and the mixed lesions.

Conclusions: Carotid atherosclerosis can be used to predict the risk of cognitive impairment. Furthermore, diagnosing and treating carotid atherosclerosis at early stage might help clinicians prevent and treat vascular cognitive impairment in nonstroke patients.

Key words: Carotid Atherosclerosis; Carotid Intima-media Thickness; Carotid Plaque; Carotid Stenosis; Cognitive Impairment; Nonstroke

INTRODUCTION

Cognitive impairment ranges from subtle deficits in cognitive function to full-blown dementia. One-six of people have cognitive impairment before an acute stroke, leading to a huge socioeconomic burden.^[1] Thus, discovering modifiable risk factors for cognitive impairment makes differences to prevent and relieve cognitive impairment. Studies have found that cerebrovascular disease played an important role on cognitive decline or dementia in patients without an obvious history of stroke.^[2] As one of the vascular contributions to cognitive impairment and dementia, the role of carotid atherosclerosis in the relation to cognitive function has provoked abundant discussions and researches in recent years, based on preclinical, neuropathology, neuroimaging,

physiological, and epidemiology studies. Recent studies have highlighted the role of carotid atherosclerosis, not only as a primary cause of cognitive impairment, but also adjuvant to the expression dementia caused by other factors, including Alzheimer’s disease (AD) and other neurodegenerative pathology.^[3-7] Carotid intima-media thickness, plaque, and stenosis determined by ultrasonography are established

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as noninvasive markers of carotid atherosclerosis. This review aimed to describe the association between carotid atherosclerosis and cognitive function using carotid plaque, intima-media thickness, and stenosis as biomarkers in stroke-free patients and to make a further illustration on the role of atherosclerosis in the progress of cognitive impairment without stroke.

COGNITIVE IMPAIRMENT IN NONSTROKE PATIENTS WITH CAROTID ATHEROSCLEROSIS

Carotid intima-media thickness and cognitive impairment

Carotid intima-media thickness is defined as the distance between the luminal–endothelial interface and the junction between the media and the adventitia on a longitudinal ultrasound image of each artery.^[4,8] As a surrogate marker of atherosclerosis, intima-media thickness levels greater than 0.9 mm were associated with atherosclerosis. Baseline intima-media thickness level has been proved to be a good independent predictor for new cognitive impairment in the middle-aged patients according to community-dwelling studies.^[9–11] In the Dallas Heart Study, a population-based multiethnic study, subclinical atherosclerosis minimally correlated with later cognitive function in middle-aged patients.^[12] A Chinese cross-sectional study of the middle-aged and older adults indicated that carotid intima-media thickness had a strong relationship with global cognitive function, especially to those older and with lower education levels, which was consistent with population-based studies in Western countries,^[13] such as the INVADE study,^[9] the Rotterdam study,^[14] and the Cardiovascular Health Study.^[15] A Framingham Offspring Study involving 1975 participants without stroke and dementia indicated that intima-media thickness of internal carotid artery, not common carotid artery, could decline both verbal and nonverbal memory performance.^[10] Elevated intima-media thickness might account for specific cognitive domains impairment including attention-executive function and memory.^[16,17] In a cohort from the Baltimore Longitudinal Study of Aging, among community-dwelling individuals without vascular and neurological diseases, carotid intima-media thickness could predict accelerated cognitive decline, particularly in the domain of verbal and nonverbal memory, as well as a test of semantic association fluency and executive function.^[18]

Carotid plaque and cognitive impairment

With the progressing deposition of cholesterol, inflammation, and cell infiltration on carotid vessel wall, plaque formation was built up. The presence of plaques is defined as a focal wall thickening or protrusion in the lumen >50% of the surrounding thickness. Carotid plaque biology and serologic biomarkers of vulnerability can be used to predict the risk of cognitive impairment. Total carotid plaque area is defined as the sum of all plaque areas.^[17,19] Plaque is scored according to the plaque numbers and properties.^[3,20] In the Tromsø study, the average plaque scores were associated with lower scores in all cognitive tests, and progression of plaque scores

was associated with lower scores in the digit-symbol coding test and the tapping test, but not with the verbal memory test.^[21] A study of ultrasound-based strain imaging and cognition assessment conducted on 75 patients including both symptomatic and asymptomatic carotid atherosclerosis illustrated that carotid plaque had a strong relationship with cognitive decline, especially with fast cognitive decline.^[22] According to the Gray-Weale classification, plaque composition was ultrasonically and histologically classified. Vulnerable plaques are defined as plaques which are highly prone to rupture with rapid progression and eventually lead to clinical events, especially the subtle cognition impairment.^[23] Histopathology experiments considered that fibrous-cap-thickness, calcification, inflammatory, infiltration and lipid core resulted in the instability of plaque. Furthermore, recent studies involving asymptomatic atherosclerosis subjects in whom used contrast-enhanced ultrasound to quantify plaque found that intraplaque neovessels, turbulent blood flow, and the elastic properties of the vessel wall emerged significance on plaque development.^[4,24,25] Study on asymptomatic patients with significant (>60%) carotid artery stenosis found that patients with increased maximum lateral strain of plaque performed poor on tasks of simple motor ability and complex motor/executive function.^[26] Among stroke-free patients, vulnerable plaque had a strong relationship with decreased cognitive function, particularly on psychomotor speed, attention, mental flexibility, but not verbal memory,^[12,27] while animal experiments based on mouse models found that vulnerable plaque impaired spatial learning and memory.^[28] It is noteworthy that the increased mortality rate might attenuate association between carotid plaque and cognitive impairment in nonstroke people.

Carotid stenosis and cognitive impairment

Carotid stenosis is defined if one or both of the following criteria are met: (1) peak systolic velocity in the tightest stenotic part was 0.2 m/s higher than the peak systolic velocity at the point of reference, or 0.1 m/s if the stenosis was located at the bifurcation or the bulb of the internal carotid artery (the distal part of the internal carotid artery, with parallel walls, was used as the point of reference); and (2) 35% reduction in the lumen diameter on a longitudinal B-mode scan is present. The criteria for categorizing artery stenosis are defined as follows: normal (<40%), mild to moderate stenosis (40–70%), and severe stenosis (>70%).^[29,30] Cognitive function is strongly related to the degree of carotid stenosis. Patients with severe carotid artery stenosis always had a lower mini-mental state examination score compared with the mild-to-moderate carotid artery stenosis group (40–70%).^[31] Patients with bilateral carotid stenoses were worse on performance of executive function, attention, and memory than unilateral carotid stenosis. The difference in cognitive function between patients with left and right carotid artery stenosis was not significant in high stenosis grade, while in lower stenosis grade, badly cognitive function was observed

in patients with left carotid stenosis than patients with right carotid stenosis.^[32] Patients with carotid stenosis often experienced subtle cognitive problems but not severe enough to impact on daily activities.^[33] However, the mild cognitive decline caused by carotid artery stenosis might lead to later dementia. Carotid stenosis was broadly considered to be correlated with general cognitive impairment.^[34] In the Framingham Offspring Study, internal carotid stenosis $\geq 50\%$ was associated with higher prevalence poorer performance on executive function.^[10] The study regarding asymptomatic carotid stenosis and cognitive function found that asymptomatic carotid stenosis was associated with overall cognitive impairment independent of known vascular risk factors and patients with stenosis had worse domain-specific scores in both learning/memory and motor/processing speed. Almost half of the patients were impaired in at least two cognitive domains.^[35] In this study, performance scores were numerically reduced for executive/visuospatial function, but it was not statistical significance. The discrepancies on specific cognitive domains might be due to the differences between sample populations, choices of cognitive tests, and analytic approaches.

MECHANISMS OF COGNITIVE IMPAIRMENT IN NONSTROKE PATIENTS WITH CAROTID ATHEROSCLEROSIS

Cerebrovascular function

Cerebrovascular function includes cerebrovascular reserve, stiffness, and cerebral blood flow.^[36] Reduction in global cerebral perfusion caused by carotid atherosclerosis especially high-grade stenosis of internal carotid arteries can produce brain dysfunction and impair cognition transiently or permanently.^[37] Reductions in cerebral blood flow by 40–50% might suppress brain activity and cause cognitive dysfunction. Accompany with increased carotid intima-media thickness, carotid arterial stiffness increased, lowering cerebral autoregulation.^[10,38] Increased intima-media thickness lowered the intracranial arterial perfusion and reduced the blood flow velocity by narrowing the vessel lumen. Consistently, arterial stiffness has previously been associated with an increased amount of white matter changes.^[39] Since there were broad consensus that increased arterial stiffness and narrowed vessel lumen synergistically caused hypoperfusion directly, possible mechanisms included not only hypoperfusion or lunar dementia but also the impairment of neuronal viability.^[40-42] Those altered neuronal viability and impaired regional functional connectivity induced by cerebrovascular function disturbance were correlated with poorer cognitive performance in patients with asymptomatic stenosis.^[7] In addition, the damaged cerebrovascular function might contribute to silent stroke, which could be detected by high resolution MRI. Beyond hypoperfusion, silent stroke might promote subtle cognitive impairment like memory decline directly.

Cerebral small-vessel disease

Cerebral small-vessel disease, including leukoaraiosis, lacunes, microinfarcts, brain atrophy, and enlarged perivascular spaces, has been proved to be crucial in the progression of vascular cognitive impairment and mixed dementia, and it might strongly associate with carotid atherosclerosis.^[43] Carotid atherosclerosis strongly associated with small cerebral vessel disease, and the pathological pathway between them could be attributed to microembolism and shared risk factors. There was a positive correlation between the degree of carotid stenosis and degree of white matter hyperintensities (WMHs) lesion burden, particularly in periventricular areas among patients without intracranial large-vessel stenosis.^[44] The increase of total WMH lesion burden has been associated with decreased cognitive performance.^[45] Hypoperfusion and inflammation are major reasons for leukoaraiosis. In addition, vulnerable plaques are more prone to microvascular changes and embolization, causing microinfarcts and silent strokes. Internal carotid artery vulnerable plaques strongly related to the amount of WMHs.^[3] Furthermore, subclinical microembolism caused cumulative brain damage, ending up with the WMHs and brain atrophy.^[41] Microinfarcts generated from plaque rupture and hypoperfusion could account for vascular cognitive decline via directly disrupting cognitive network.^[46]

Mixed lesions

As carotid atherosclerosis always overlap with neurodegenerative pathology, the relationship between them still needs to be investigated in more studies due to multiplicity of underlying pathology.^[44] The most consistent histologic findings about carotid atherosclerosis, especially plaque, were that carotid atherosclerosis could prolong activation of microglial and astrocytes. Activated microglial elaborate interleukin-1 and other cytokines appeared to precipitate cognitive impairment by interference with synaptic plasticity.^[47] Chronic inflammation with microglial activation has been identified as a causative factor in several neurodegenerative diseases^[48] and has been associated with cognitive decline.^[49] Subclinical carotid atherosclerosis was associated with worse cognition among those at higher risk for Alzheimer's disease. The attributable causes might be that cholesterol embolism could disrupt the blood-brain barrier and elicit an immune response,^[16] leading to the deposition amyloid. Thus, the linkage in microembolization and chronic inflammation suggested a new mechanism for microembolic events and cognitive decline.^[19,50] Furthermore, cerebral hypoperfusion and hypoxia caused by carotid atherosclerosis also destabilize neurons and promote formation of neurofibrillary tangles and amyloid plaques.^[4,51]

CONCLUSIONS

Carotid atherosclerosis is an independent vascular risk factor for cognitive impairment in nonstroke patients. Carotid atherosclerosis emerges an importance in the onset, severity, and progression of cognitive dysfunction. It can not only

impair the subtle general cognitive function but also decrease the specific domain such as memory, motor function, visual perception, attention, and executive function, which are still on studying. Carotid atherosclerosis deteriorates cognitive function through the impairment of structural and functional integrity of the brain. The possible mechanisms of cognitive impairment caused by atherosclerosis are analyzed as follows. First, carotid atherosclerosis might lead to brain hypoperfusion, lacunar infarction, and atrophy through lowering cerebrovascular reserve, narrowing vessel lumen, and reduce the blood flow velocity. Then, carotid atherosclerosis might share the same proinflammatory state, metabolic dysfunction, and pathogenic factors with cognitive impairment. Furthermore, the small-vessel diseases such as microinfarcts, white matter lesions, and lacunes caused by microembolisms due to plaque rupture and subsequent silent stroke provide us new ideas about the mechanisms. Besides, as a typical manifestation of cerebrovascular disease, the interaction between carotid atherosclerosis and neurodegenerative pathophysiology has taken more and more attention.

Overall, there is a broad consensus that carotid atherosclerosis has a strong relationship with vascular cognitive decline in patients before or without clinical stroke, but the detailed results have been inconsistent, especially on which cognitive domains are most affected. However, some researchers still doubt the direct correlation between carotid disease and vascular cognitive impairment in patients without stroke. To their opinions, atherosclerosis is a systematic inflammatory disease in whole body. Carotid atherosclerosis, easily probed by ultrasonography, just reminds us the state of the intracranial vascular, which is the direct cause of cognitive impairment instead of carotid disease itself. The discrepancies might be explained by the limitation of the imaging detection, research methods, and endpoints. However, the knowledge on the isolated impact of neurologically asymptomatic carotid atherosclerosis on cognitive function is limited because these patients tend to have concomitant vascular risk factors with potential confounding vascular cognitive impairment. The detailed mechanisms still need to be further explored to help clinicians prevent, detect, and treat cognitive impairment in nonstroke carotid atherosclerosis patients.

This review described the latest researches regarding the interactive effects of carotid atherosclerosis and cognitive impairment in nonstroke people. Carotid atherosclerosis is associated with the onset, severity, and progression of cognitive dysfunction and can be used to predict the risk of cognitive impairment in stroke-free patients. Possible mechanisms of cognitive impairment in nonstroke patients with carotid atherosclerosis include systemic global cerebrovascular function, small-vessel diseases, and the mixed lesions induced by interactions between vascular risk factors and neurodegenerative pathophysiology, which still need to be further investigated in future.

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Conflicts of interest

There are no conflicts of interest.

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