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Impact of Coronary Artery Disease on Long-Term Cognitive Outcome after Carotid Endarterectomy

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Abstract

Objective: Carotid stenosis and coronary artery disease (CAD) are associated with cognitive decline, but little is known about the impact of CAD on cognitive outcome after carotid endarterectomy (CEA). The aim of this study was to assess the long-term cognitive outcomes after CEA in patients with CAD and to identify causative risk factors for cognitive decline.

Methods: Among 36 consecutive patients with CAD who had undergone CEA between February 2016 and June 2018, and 45 patients without CAD who had undergone CEA during the same period, cognitive functions were studied using the Neurobehavioral Cognitive Status Examination (Cognistat) and the Frontal Assessment Battery (FAB). Cognitive decline was defined as both FAB total score below the cutoff value and severe impairment in at least one domain on Cognistat.

Results: Cognitive decline was evident in 27.8% of patients with CAD at a mean of 7.2 years after CEA, and in 8.9% of patients without CAD. Comprehension, memory, and conceptualization were significantly impaired in patients with CAD compared to patients without CAD (p=0.0274, 0.0392, and 0.0113, respectively).In patients with CAD, univariate analysis revealed that deep white matter hyperintensity (DWMH) and chronic kidney disease associated with cognitive decline (odds ratio (OR) 32.2, 95% confidence interval (CI) 3.20-323.66, p=0.0032; OR 6.11, 95%CI 1.13-33.19; p=0.0360, respectively).

Conclusions: This result may be useful to better identify individuals at high risk of cognitive decline long after CEA.

Keywords: carotid endarterectomy; coronary artery disease; cognitive decline; deep white matter hyperintensity; chronic kidney disease

Introduction

Carotid stenosis and coronary artery disease (CAD) are associated with cognitive decline, as both are phenotypes of atherosclerosis and share common vascular risk factors. Carotid stenosis can cause cognitive decline through hemodynamic and embolic mechanisms. Carotid endarterectomy (CEA) is expected to maintain or improve cognitive function by reversing the pathological conditions, but CEA itself carries risks of cognitive decline due to micro embolism arising during the surgical procedure, hypoperfusion during carotid artery clamping, general anesthesia, and postoperative hyperperfusion [1]. CEA reduced the frequency of microemboli from 25.0% to 17.9% at 1 year after surgery[2], suggesting that risk of cognitive decline persists even after CEA. Thus, CEA can cause both cognitive improvements and declines, but whether these complex interactions ultimately result in an improved or deteriorated cognitive function remains unclear [3].

On the other hand, patients with CAD risk of cognitive impairment[4], and cognitive decline is a common complaint amongthesepatients [5,6]. However, little is known about the impact of CAD on cognitive outcome after CEA. This study aimed to assess the long-term cognitive outcomes after CEA in patients with CAD and to identify causative risk factors for cognitive decline.

Methods

Patients

Thirty-six patients with CAD who had undergone CEA and were admitted to our institution between February 2016 and June 2018 for periodic follow-up were invited to participate in this study. Clinical data were obtained from patients by retrospective chart review. CAD was confirmed in all but 2 patients by coronary angiography showing coronary stenosis with at least 75% narrowing in at least one vessel. CAD was identified in the other 2 patients by myocardial scintigraphy instead of coronary angiography because of renal dysfunction or contrast agent allergy. Clinical data from45 patients without CAD who had undergone CEA and were admitted during the same period were collected as control data. None of the 45 controls had any history of chest symptoms or any evidence of myocardial ischemia as assessed from both electrocardiography and transthoracic echocardiography. All patients underwent CEA for severe carotid stenosis or unstable plaque under general anesthesia with propofol. Surgical indications for carotid stenosis were as follows: linear stenosis >70%, area stenosis >90%, and peak flow velocity in the internal carotid artery (ICA) >200 cm/s on transcranial color-coded sonography. Exclusion criteria were the presence of aphasia or physical deficits preventing the conduct of neurocognitive examinations. Patients who had previously undergone neurocognitive assessment were not included in this study, to avoid any risk of practice effect.

Cognitive assessment

The Japanese versions of Cognistat and the Frontal Assessment Battery (FAB) were adopted to assess cognitive functions [7–10]. Cognisant consists of 10 sub-components and severity of impairment in each cognitive domain was defined as follows: score ≥9, normal; 8, mild impairment; 7, moderate impairment; ≤6, severe impairment[8]. The FAB consists of 6 sub-components, and the following cutoff values for total score were applied: < 60 years old, 15; 60-69 years old, 13; ≥ 70 years old, 11[11]. Cognitive decline was defined as both FAB total score below the cutoff and severe impairment in at least one domain of Cognistat.

Magnetic resonance imaging (MRI)

All patients underwent MRI on the same day or the day before the cognitive examination to assess white matter lesions of the brain. Deep White-Matter Hyperintensity (DWMH) and periventricular hyperintensity (PVH) on T2-weighted imaging were classified using Fazekas grade [12]. Intracranial atherosclerosis was defined as >50% stenosis of the ICA, middle cerebral artery, or anterior cerebral artery on MR angiography.

Statistical analysis

Age was represented as mean ± standard deviation. Other data were represented as median and interquartile range, except where indicated otherwise. Statistical analysis was performed using the Wilcoxon rank-sum test for non-parametric data. Differences in binary variables were assessed using Pearson's chi-square test. Univariate analysis was used to evaluate associations between variables and cognitive decline. One-way analysis of variance was used to compare cognitive test scores among DWMH grades. Differences were considered significant for values of $p < 0.05$. All statistical analyses were performed using JMP Pro version 13.2software (SAS Institute, Cary, NC).

Ethics

The study was approved by the National Hospital Organization Kyushu Medical Center Ethical Review Board (18C194).

Results

Baseline characteristics

Patients with CAD comprised 29 men and 7 women (angina pectoris, n=17;myocardial infarction, n=10;asymptomatic myocardial ischemia, n=6;silent myocardial infarction, n=3). Three patients had undergone coronary artery bypass grafting(-CABG) alone before CEA, and 2 had undergone CABG and percutaneous coronary intervention (PCI) before CEA. Nine patients had undergone PCI alone before CEA and 1 had undergone PCI before and after CEA. Two patients had undergone CABG alone after CEA and 1 had undergone CABG and PCI after CEA. Four patients had undergone PCI alone after CEA. In CAD patients who had not undergone CABG nor PCI, coronary angiography showed 50-75% stenosis in the left anterior descending branch with or without more than 75% narrowing in the other branches, with the exception of the 2 patients who did not undergo coronary angiography.

Table 1 shows that no significant differences between patients with and without CAD were noted in any baseline data except left carotid artery stenosis on examination. Left carotid stenosis was more severe in patients with CAD than in patients without CAD (p=0.0164). Most patients were receiving pharmacologic therapy for hypertension and dyslipidemia and were taking an antiplatelet agent. Brain infarction >3 cm in diameter was observed in 19.4% of CAD patients and 22.2% of patients without CAD at the examination. Mean Fazekas DWMH grade and PVH grade did not differ between patients with and without CAD. Table 2 shows that no significant differences between patients with and without CAD were noted in symptomatic onset, operated side, postoperative complications, or intraoperative use of an internal shunt.

Table 1. Baseline demographic characteristics at the examination

	With CAD (n=36)	Without CAD (n=45)	P value
Age (years)	77.8 ± 5.3	75.7 ± 6.5	0.1224
Follow-up period (years)	7.0 [5.0, 9.0]	5.1 [4.0, 7.1]	0.1174
Male (%)	29 (80.6)	37 (82.2)	0.8478
Medical history (%)			
Hypertension	34 (94.4)	42 (93.3)	0.8364
Diabetes mellitus	16 (44.4)	23 (51.1)	0.5507
Dyslipidemia	35 (97.2)	40 (88.9)	0.1547
Chronic kidney disease	11 (30.6)	7 (15.6)	0.1066
Atherosclerosis obliterans	6 (16.7)	2 (4.4)	0.0669
Atrial fibrillation	3 (8.3)	1 (2.2)	0.2072
Smoking history	26 (72.2)	35 (77.8)	0.5645
Alcohol >40 g/day	4 (11.1)	1 (2.2)	0.0986
Use of antiplatelet	35 (97.2)	44 (97.8)	0.8728
Use of anticoagulant	4 (11.1)	2 (4.4)	0.2549
Dementia	0	3 (6.7)	0.1144
Brain infarction	7 (19.4)	10 (22.2)	0.7603
CA stenosis at examination (%)			
Right	41.8 [0, 54.5]	47.0 [0, 60.4]	0.3283
Left	52.0 [38.6, 59.0]	37.0 [0, 53.1]	0.0164
Contralateral ICA occlusion (%)	1 (2.8)	1 (2.2)	0.8728
Intracranial atherosclerosis (%)	8 (22.2)	9 (20.0)	0.8072
DWMH grade	1 [1, 2]	1 [0, 1]	0.1266
DWMH grade ≥2 (%)	12 (33.3)	9 (20.0)	0.1736
PVH grade	1 [0, 1.8]	1 [0, 2]	0.5956
PVH grade ≥2 (%)	8 (22.2)	12 (26.7)	0.6448

CAD, coronary artery disease; CA, carotid artery; ICA, internal carotid artery; DWMH, deep white matter hyperintensity; PVH, periventricular hyperintensity

Table 2.Perioperative demographic characteristics.

	With CAD (n=36)	Without CAD (n=45)	P value
Symptomatic onset (%)	18 (50.0)	32 (71.1)	0.0521
Operated side (%)			0.1298
Right	23 (63.9)	21 (46.7)	
Left	9 (25.0)	21 (46.7)	
Bilateral	4 (11.1)	3 (6.7)	
Hyperintensity on postoperative DWI (%)	3 (8.3)	6 (13.3)	0.4768
Postoperative HP (%)	0	2 (4.4)	0.2003
Postoperative HPS (%)	0	1 (2.2)	0.3681
Use of internal shunt (%)	13 (36.1)	18 (40.0)	0.7205

CAD, coronary artery disease; DWI, diffusion-weighted imaging; HP, hyperperfusion; HPS, hyperperfusion syndrome

Cognitive assessment

No significant difference in total Cognistat score or total FAB score was evident between patients with and without CAD. Scores for comprehension, memory, and conceptualization were significantly lower in patients with CAD than in patients without CAD (p=0.0274, 0.0392, and 0.0113, respectively; Table 3). Cognitive decline, defined as FAB total score below the cutoff along with severe impairment in at least one domain on Cognistat, was seen in 8 patients with CAD (27.8%), and in 4 patients without CAD (8.9%).

In patients with CAD, univariate analysis revealed that DWMH and chronic kidney disease (CKD) were associated with cognitive decline (odds ratio (OR) 32.2, 95% confidence interval (CI) 3.20-323.66, p=0.0032; OR 6.11, 95%CI 1.13-33.19; p=0.0360, respectively; Table 4). The association between DWMH and CKD was not evident (p= 0.3061), and the association between DWMH and cognitive decline persisted after adjusting for CKD (p= 0.0004). Table 5 describes cognitive test scores and DWMH grades in patients with CAD. Total Cognistat score, total FAB score, scores for comprehension, similarity, programming, and sensitivity to interference declined as Fazekas DWMH grade increased. Univariate analysis showed no association between carotid stenosis and cognitive decline (p=0.1739 for right carotid stenosis; p=0.1954 for left carotid stenosis).

Discussion

Cognitive decline was evident in 27.8% of patients with CAD at a mean of 7.2 years after CEA, and in 8.9% in patients without CAD at a mean of 6.1 years after CEA. We also found that comprehension, memory, and conceptualization were impaired compared to patients without CAD. DWMH and chronic kidney disease were risk factors or predictors for cognitive decline long after CEA. In particular, DWMH was associated with declines in several specific cognitive domains.

Carotid stenosis, CAD, and cognitive decline share modifiable cardiovascular risk factors such as obesity, diabetes, smoking, hypertension, physical inactivity, and dyslipidemia [13,14]. Our results indicated that cognitive decline long after CEA was more common in patients with CAD compared to patients without CAD. Left carotid artery stenosis at examination was more severe among CAD patients, suggesting that atherosclerosis might be more critical in patients with CAD than in those without. However, no significant differences were evident in intracranial atherosclerosis, DWMH, CKD, arteriosclerosis obliterans, or cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia between patients with and without CAD. On the other hand, CAD appeared to be associated with cognitive decline. A study of 1101 patients with CAD aged >65 years showed the prevalence of cognitive impairment was 62% [15]. The presence of CAD accelerated cognitive decline as measured with the Mini-Mental State Examination by about 66% in 118 patients with Alzheimer's or mixed dementia [16].

Table 3. Cognitive examination

	With CAD (n=36)	Without CAD (n=45)	P value
Cognistat			
Total score	94 [82, 97.8]	96 [92, 100]	0.0966
Orientation	10 [9.3, 10]	10 [10, 10]	0.5091
Attention	10 [6, 10]	10 [8, 10]	0.3698
Comprehension	10 [7, 10]	10 [10, 10]	0.0274
Repetition	11 [8, 11]	11 [8.5, 11]	0.2108
Naming	10 [10, 10]	10 [9, 10]	0.5799
Construction	9 [7.3, 11]	9 [8, 11]	0.3634
Memory	7.5 [6, 9]	8 [7, 10]	0.0392
Calculation	10 [8.5, 10]	10 [10, 10]	0.1122
Similarity	10 [9, 10]	10 [9, 10]	0.1551
Judgment	10 [9, 11]	10 [10, 11]	0.4356
FAB			
Total score	13 [11, 16]	14 [12, 16]	0.2093
Conceptualization	2 [1, 2]	2 [2, 2]	0.0113
Mental flexibility	2 [1, 2]	2 [1.5, 3]	0.1963
Programming	2 [1, 3]	2 [1, 3]	0.7588
Sensitivity to interference	3 [3, 3]	3 [3, 3]	0.4302
Inhibitory control	2 [1, 3]	2 [1, 3]	0.4740
Environmental autonomy	3 [3, 3]	3 [3, 3]	0.2743
Education (years)	12 [9, 16]	12 [12, 16]	0.2074
mRS at examination	0 [0, 1]	0 [0, 1]	0.8132
Barthel index at examination	100 [100, 100]	100 [100, 100]	0.8328

CAD, coronary artery disease; FAB, frontal assessment battery; mRS, modified Rankin scale

Table 4. Univariate analysis for predictors of cognitive decline in patients with coronary artery disease.

Variable	Odds ratio (95% Confidence interval)	P value
Deep white matter hyperintensity	32.2 (3.20-323.66)	0.0032
Chronic kidney disease	6.11 (1.13-33.19)	0.0360
Age	0.86 (0.73-1.03)	0.0720
Education	1.20 (0.95-1.52)	0.1235
Alcohol	4.33 (0.50-37.26)	0.1816
Arteriosclerosis obliterans bypass	2.78 (0.38-20.50)	0.3164
Coronary artery bypass graft	0.43 (0.05-4.12)	0.4631
Male	0.65 (0.10-4.23)	0.6541
Current smoking	1.53 (0.24-9.95)	0.6541
Periventricular hyperintensity	1.22 (0.20-7.68)	0.8305
Left ventricular ejection fraction	0.93 (0.78-1.12)	0.8315
Smoking history	1.20 (0.20-7.25)	0.8425
Percutaneous coronary intervention	1.00 (0.21-4.81)	1.0000

Table 5. Cognitive examination by deep white matter hyperintensity in patients with coronary artery disease.

	Deep white matter hyperintensity grade				P value
	0 (n=7)	1 (n=17)	2 (n=4)	3 (n=8)	
Cognistat					
Total score	97 [95, 99]	95 [88.5, 98.5]	76 [71.5, 89.5]	84 [68.75, 94]	0.0086
Orientation	10 [10, 10]	10 [9.5, 10]	9.5 [6, 10]	10 [6.75, 10]	0.3257
Attention	10 [6, 10]	10 [8, 10]	6 [3.75, 9]	8 [1.5, 10]	0.2782
Comprehension	10 [10, 10]	10 [8.5, 10]	7 [4.75, 9.25]	8.5 [4, 10]	0.0320
Repetition	11 [10, 11]	11 [8, 11]	7 [6.25, 10]	10.5 [6, 11]	0.2264
Naming	10 [10, 10]	10 [10, 10]	9 [7.5, 9.75]	10 [9.25, 10]	0.1697
Construction	9 [8, 11]	9 [8, 11]	7 [6, 8.75]	7.5 [6, 10.25]	0.0581
Memory	8 [5, 9]	8 [6, 9]	8 [6.25, 9]	6.5 [5.25, 8]	0.6135
Calculation	10 [10, 10]	10 [10, 10]	9 [6.5, 10]	9 [6.5, 10]	0.1334
Similarity	10 [9, 10]	10 [9, 10]	7.5 [6.25, 9.5]	9 [8.25, 10.75]	0.0418
Judgment	10 [9, 12]	10 [10, 11]	9.5[9, 10]	9.5 [9, 11]	0.5093
Frontal assessment battery					
Total score	14 [13, 17]	15 [12.5, 16]	9.5 [8.25, 13]	10.5 [8.5, 11.75]	0.0002
Conceptualization	2 [2, 2]	2 [2, 2]	0 [0, 1.5]	2 [1, 2]	0.0059
Mental flexibility	2 [2, 3]	2 [1, 2]	2 [1.25, 2]	1.5 [0.25, 2.75]	0.1820
Programming	3 [1, 3]	3 [2, 3]	1.5 [1, 2]	1 [0.25, 2.75]	0.0311
Sensitivity to interference	3 [3, 3]	3 [3, 3]	3 [0.75, 3]	2 [0.25, 3]	0.0223
Inhibitory control	3 [2, 3]	2 [1, 3]	1.5 [0.25, 2]	1 [1, 2.75]	0.0880
Environmental autonomy	3 [3, 3]	3 [3, 3]	3 [3, 3]	3 [3, 3]	0.3309

A recent meta-analysis of 10 prospective cohort studies representing 24,801 persons indicated that CAD was associated with increased risk of cognitive decline (OR = 1.45, 95%CI = 1.21–1.74, p<0.001)[17].

We found that comprehension, memory, and conceptualization were significantly lower in patients with CAD compared to patients without CAD. Attention, memory, executive function, visuospatial orientation, psychomotor speed, and fluency improved shortly after CEA [2,18–21], while language, working memory, and global cognition deteriorated [1,22–25]. These were all short-term changes, and long-term changes in cognitive domains after CEA are still unknown. On the other hand, global cognition, verbal memory, and executive function declined in CAD patients who were cognitively intact at baseline after a mean follow-up of 6.9 years [26]. Working memory, processing speed, cognitive inhibition, flexibility, and long-term verbal memory were impaired even in patients with stable CAD compared to age-matched old health controls [27].

Several studies have reported various risk factors of cognitive decline short after CEA. Age, education, intelligent quality, brain atrophy, preoperative symptoms, and white matter hyperintensity were associated with cognitive changes at 1-6 months after CEA [22,28,29], but factors relating to long-term cognitive changes after CEA are still unclear. Post-hoc meta-regression analyses showed that the association between CAD and cognitive decline was unchanged after adjusting for risk factors such as diabetes, hypertension, and dyslipidemia, suggesting that this association cannot be solely explained by cardiovascular risk factors [17]. A systematic review identified CABG, apolipoprotein E4, left ventricular ejection fraction, medication use, and hormones and biomarkers as predictors of cognitive decline in patients with CAD [30].Conversely, a prospective longitudinal study found no significant differences in long-term cognitive outcomes among CAD patients treated surgically with on-pump CABG (n = 152) or off-pump CABG (n = 75)) or non-surgically (n = 99)[6]. This is consistent with our results from univariate analysis.

Our results indicated that DWMH was significantly associated with cognitive decline and DWMH grade was associated with declines in several cognitive domains among CAD patients long after CEA. Cerebral white matter hyperintensity (WMH) has been shown to be strongly associated with an increased risk of cognitive impairment [31]. Community-based epidemiologic

studies have revealed that WMH and silent brain infarct (SBI) were associated with cerebrovascular risk factors and cognitive decline [32–35]. One study reported that CEA prevented increases in WMH at 1 year after surgery in 14 patients who were already cognitively impaired preoperatively [2]. Another study revealed that WMH was one of the differences between cognitive responders and non-responders at 1 year after CEA, but WMH was not independent associated with cognitive decline in multivariate analysis [22].On the other hand, a cross-sectional study showed that cerebral white matter microstructural integrity was associated with executive function impairment in 49 patients with CAD [36]. Longitudinal studies demonstrated that progression of WMH grade was associated with declines in overall cognitive function and several specific domains[34, 35], but the associations between CAD and cognitive decline persisted after adjusting for both baseline levels and changes in WMH and SBI, indicating that these associations are not fully explained by MRI-measured WMH and SBI [26].

One strength of this study was a long follow-up. We evaluated neurocognitive functions in patients with CAD at a mean of 7.2 years after CEA, using two representative cognitive batteries. This study has several limitations. First, the study was cross-sectional in design. When the neurocognitive function starts to decline and the influence of progressive DWMH changes over time on cognitive decline in CAD patients are unknown. To clarify sequential changes in neurocognitive function, longitudinal studies are needed. Second, the sample size was relatively small. We could not perform multivariate analysis for predictors of cognitive decline.

Conclusions

Our findings indicate that long-term neurocognitive outcomes in several cognitive domains were inferior in patients with CAD compared to those in patients without CAD.

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