

# Does cerebral large-artery disease contribute to cognitive impairment?

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## ABSTRACT

**Purpose:** Although many patients with cerebral large-artery disease (CLAD) show impaired cognitive performance, the risk factors remain unclear in this population. The objective of this study was to evaluate cognitive impairment and its risk factors in patients with CLAD.

**Methods:** We recruited non-demented patients with CLAD from our hospital. CLAD was defined as occlusion or stenosis of over 50% in the carotid artery or middle cerebral artery. We collected patients' biographical data and vascular lesion and imaging data, including periventricular hyperintensity (PVH) and cerebral perfusion. The patients were divided into two groups: cognitive impairment-plus (CoI+) and normal (CoI-) groups, according to their Montreal Cognitive Assessment (MoCA) scores, with a cut-off value of 26. The factors associated with cognitive impairment were examined.

**Result:** Of the 176 patients with CLAD (mean age  $70.2 \pm 8.3$ , 40 female), 136 (77.2%) were classified as cognitively impaired. Multivariate analysis indicated that the CoI+ group was associated with older age (odds ratio (OR): 1.09,  $P = 0.011$ ), drinking habit (OR: 7.15,  $P = 0.003$ ), increased PVH (OR: 3.46,  $P = 0.003$ ), and decreased cerebral perfusion (OR: 0.897,  $P = 0.007$ ). Analyses of the MoCA subscores indicated that attention, memory, and orientation were impaired in the CoI+ group.

**Conclusion:** Impaired cognition was observed in some of the non-demented patients with CLAD. Older age, drinking habit, severe PVH and decreased cerebral perfusion contributed to their poor cognitive performance. Strict treatment of atherosclerosis and intervention for CLAD might be necessary to prevent cognitive decline in these patients.

## 1. Introduction

Along with the increasingly elderly population in Japan, both vascular dementia and Alzheimer's disease are important issues to be tackled. Vascular dementia includes small-vessel, infarct, hemorrhagic, and hereditary vascular dementia, and Alzheimer's disease with cardiovascular disease [1]. Studies have investigated whether cerebral large-artery disease (CLAD) and atherosclerotic risk factors contribute to mild cognitive decline or vascular dementia [1–6]. These findings are important because they allow us to decide which patients with CLAD should be treated by strictly controlling their atherosclerotic risk factors or should be considered for intervention. However, they have not been sufficiently tested [2,3]. CLAD might induce cognitive decline because of the risk of ischemic stroke, cerebral hypoperfusion, white matter lesions, and microembolization. It also remains uncertain which of these factors modifies which cognitive function.

The purpose of the current study was to elucidate the prevalence and characteristics of impaired cognitive performance in patients with

CLAD.

## 2. Material and methods

We prospectively registered patients who were admitted to Fukuoka University Hospital from October 2011 to December 2013 to identify those with cerebrovascular diseases. CLAD was defined as stenosis or occlusion of 50% or more in either the carotid artery (CA) or middle cerebral artery (MCA). The degree of stenosis was measured by computed tomography angiography or carotid ultrasound. We excluded patients who fulfilled the diagnostic criteria for dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [7]. The study protocol was approved by the Ethics Committee of Fukuoka University Hospital. Written informed consent was obtained from all patients.

We reviewed patients' medical records to record atherosclerotic risk factors such as age, gender, hypertension, diabetes mellitus, hyperlipidemia, current smoking habit, and current drinking habit. Hypertension

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was defined as systolic blood pressure of > 140 mmHg, diastolic blood pressure of > 90 mmHg, or current use of antihypertensive agents. Diabetes mellitus was diagnosed as a fasting glucose level of over 126 mg/dL, a hemoglobin A1c concentration higher than 6.5%, or current use of hypoglycemic medication. Hyperlipidemia was determined as a total cholesterol concentration higher than 220 mg/dL or current use of cholesterol-lowering medication. With respect to current smoking and drinking habits, those who had not smoked or drank alcohol for over a year were categorized as non-smokers and non-drinkers, respectively. We collected data on the number of years of education, as this may also influence the risk of cognitive impairment. Neurological deficits within 120 days were also determined. Patients with CLAD on both sides were defined as having bilateral lesions. CLAD was categorized as right, left, or bilateral. The presence of tandem lesions was determined in those with both CA and MCA lesions on either side.

Cerebral perfusion was measured by Tc-99 m ECD SPECT. The SPECT scan was started 5 min after the administration of 600 MBq of Tc-99 m ECD, and data were collected for 20 min using a 3-head gamma camera. All of the patients included in this study underwent an MRI scan. Deep subcortical white matter hyperintensity (DSWMH) and periventricular hyperintensity (PVH) were evaluated using fluid-attenuated inversion recovery images. The severities of DSWMH and PVH were stratified according to the report by Shinohara et al. [8]. The assessments were performed by two experienced neurologists (S.K. and T.O.) and agreements were reached between them in all cases.

The Montreal Cognitive Assessment (MoCA) is a well-refined tool for examining cognitive function, especially in patients with cognitive impairment related to stroke. The MoCA is useful for the precise evaluation of impaired cognitive performance in CLAD patients [9–11]. To address patients' cognitive functions, the Japanese version of the MoCA was administered by an experienced speech therapist (J.W.) [9]. The MoCA is a 10-min cognitive screening tool used to detect impaired cognitive performance. One additional point was added to the scores of patients with 12 years of education or less [12]. The MoCA was administered before patients who were due to undergo carotid endarterectomy or carotid arterial stenting received the intervention. Cognitive impairment was defined as a MoCA score of 25 or less. The patients were divided into two groups: CoI + and CoI -. Total MoCA scores were divided into six subscores according to the previous report [13]: visuospatial (4 points), executive (4 points), attention (6 points), language (5 points), memory (5 points), and orientation (6 points).

### 2.1. Statistics

First, univariate analyses were conducted to assess the differences in patients' background characteristics, vascular lesion characteristics, and imaging findings between the CoI + and CoI - groups. The factors that were associated with cognitive impairment with  $P$  values of < 0.10 in the univariate analyses were then entered into a logistic regression analysis. Patients were divided on the basis of each factor associated with cognitive impairment, and all of the MoCA subscores were then compared. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22.0, and  $P$  values of 0.05 were considered statistically significant.

### 3. Results

We registered 176 patients with CLAD in our study. Of these, 136 (77.2%) belonged to the CoI + group, while the remaining 40 (22.8%) scored 26 or more and were assigned to the CoI - group.

Table 1 compares the background characteristics, vascular lesion characteristics, and imaging findings between the CoI + and CoI - groups. Univariate analyses indicated that those in the CoI + group were significantly older, had fewer years of education, and were more likely to have a drinking habit. Patients in the CoI + group were more

**Table 1**  
Patient characteristics and imaging findings in the CoI + and CoI - groups.

	CoI + (n = 136)	CoI- (n = 40)	P
Age (years)	72 (67–78)	66 (58–71)	< 0.001*
Sex (man %)	106(78%)	30(75%)	0.399
Hypertension	114(84%)	29(73%)	0.107
Diabetes mellitus	52(38%)	15(38%)	0.933
Dyslipidemia	89(65%)	26(65%)	1
Smoking habit	38(28%)	10(25%)	0.714
Drinking habit	43(32%)	4(10%)	0.007
Years of education	12 (9–14)	12 (12–16)	0.005*
Neurological deficits within 120 days	51(38%)	20(50%)	0.157
Tandem lesion	15(11%)	3(8%)	0.576
Opposite lesion	50(37%)	16(40%)	0.709
Lesion of CA or MCA	–	–	0.001
MCA	15(11%)	14(35%)	
CA	98(88%)	18(60%)	
Tandem lesion	1(0.7%)	1(2.5%)	
Side of the stenosis	–	–	0.841
Right	59(43%)	18(45%)	
Left	54(40%)	14(35%)	
Bilateral	23(17%)	8(20%)	
Cerebral perfusion (ml/min/100 g)	34.3 (31.5–37.9)	37.7 (34.9–44.6)	< 0.001*
Degree of ICA stenosis (%)	80.0 (62.8–95.0)	73.5 (56.0–100)	0.692*
PVH	1.0 (0–1)	0.0 (0–0)	< 0.001*
DSWMH	2.0 (1–3)	2.0 (1–2)	0.014*

Data are median (range) or no. (%) of patients. \* indicates that the Mann-Whitney  $U$  test was used. MCA; middle cerebral artery, CA; carotid artery, PVH; periventricular hyperintensity, DSWMH; deep subcortical white matter hyperintensity.

**Table 2**  
Logistic regression analysis for the risk factors associated with cognitive impairment.

	OR	CI	P
Age	1.09	1.02–1.16	0.011
Sex	0.77	0.23–2.63	0.68
Hypertension	1.03	0.31–3.40	0.96
Duration of education	0.85	0.71–1.03	0.107
Current drinking habit	7.15	1.93–26.46	0.003
Neurological deficits within 120 days	0.48	0.18–1.28	0.15
Lesion (ICA)	1.27	0.45–3.55	0.65
Lesion side	1.15	0.62–2.15	0.66
PVH	3.46	1.53–7.85	0.003
DSWMH	0.64	0.33–1.25	0.19
Cerebral perfusion (ml/100 g/min)	0.897	0.83–0.97	0.007

OR; odds ratio, CI; confidential interval.

likely to have CA lesions than MCA lesions. Concerning the imaging findings, the degree of stenosis did not statistically differ between the two groups. However, cerebral perfusion was more diminished in the CoI + group ( $P < 0.001$ ), and PVH and DSWMH were more severe in the CoI + group ( $P < 0.001$ ,  $P = 0.014$ , respectively).

Logistic regression analysis indicated that the factors associated with cognitive impairment were age (odds ratio (OR): 1.09,  $P = 0.011$ ), drinking habit (OR: 7.15,  $P = 0.003$ ), PVH (OR: 3.46,  $P = 0.003$ ), and cerebral perfusion (OR: 0.897,  $P = 0.007$ ) (Table 2).

The MoCA subscores were compared after dividing patients by age (under 65, 65 to 74, and 75 or older: Fig. 1), drinking habit, PVH severity (0, 1 to 2, and 3 to 4: Fig. 3) or cerebral perfusion (under 30, 30 to 39.9, and 40 or more: Fig. 2), and drinking habit (Fig. 4). Attention, memory, and orientation scores were significantly associated with age, PVH severity, and cerebral perfusion, but none of the subscores was associated with drinking habit.

### 4. Discussion

The purpose of the current study was to assess the prevalence of

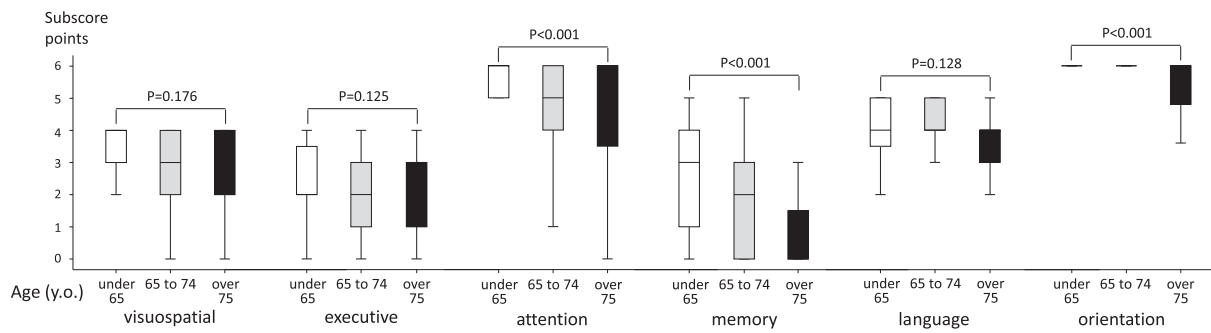


Fig. 1. MoCA subscores by age category. Attention, memory, and orientation scores were significantly lower in the older than the younger age group.

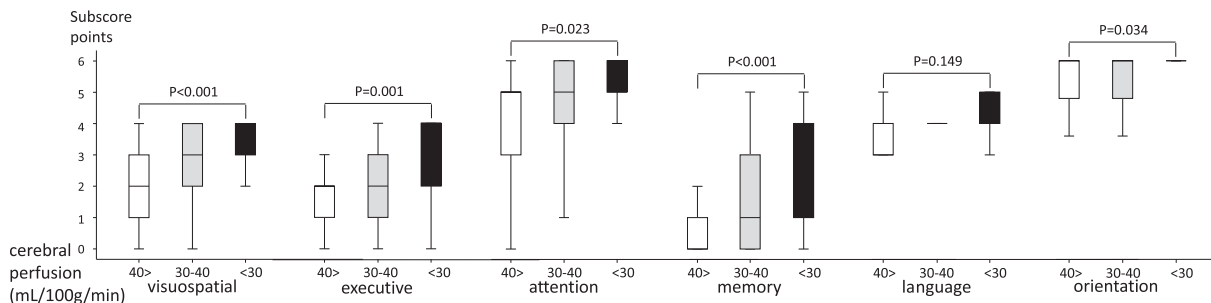


Fig. 2. MoCA subscores by cerebral perfusion category. Visuospatial, executive function, attention, memory, and orientation scores were significantly lower in patients with cerebral hypoperfusion.

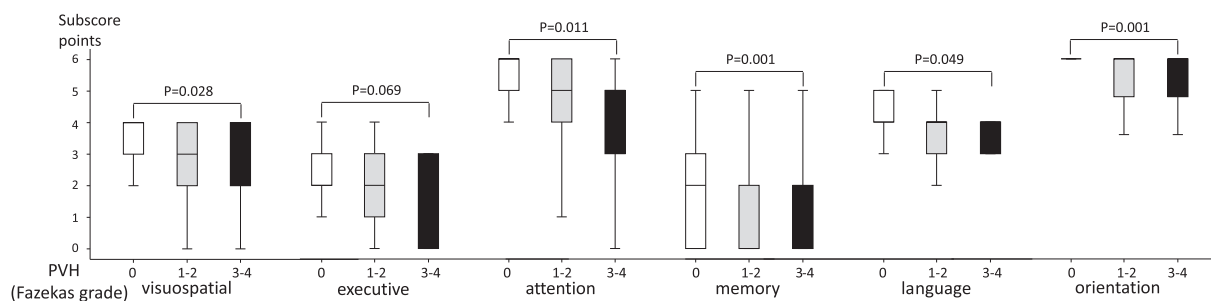


Fig. 3. MoCA subscores by severity of PVH. Visuospatial, attention, memory, and orientation scores were significantly lower in patients with severe PVH.

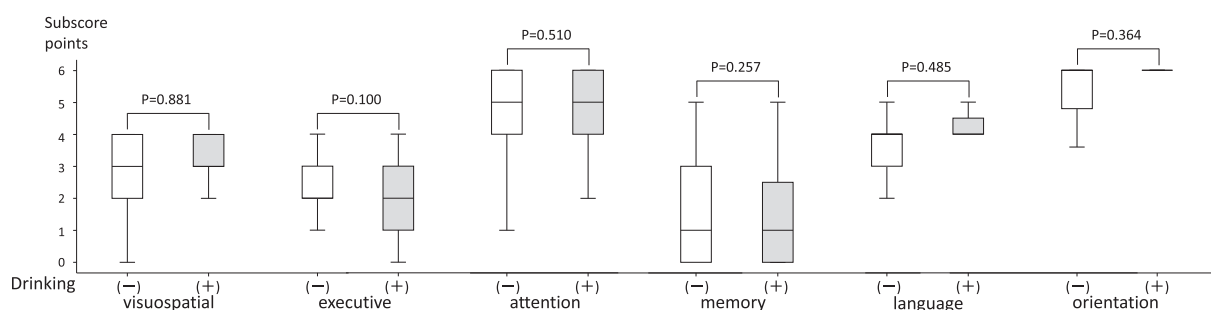


Fig. 4. MoCA subscores by drinking habit. None of the scores significantly differed between patients who did and did not drink alcohol.

cognitive decline in patients with CLAD and the associated risk factors. The results indicated a surprisingly high prevalence of cognitive decline. The factors associated with total MoCA scores were age, drinking habit, PVH, and cerebral perfusion. An analysis of MoCA subscores indicated that attention, memory, and orientation were significantly affected by older age, severe PVH, and cerebral hypoperfusion, but not drinking habit.

Several studies have addressed the association between the pathophysiology of cognitive decline and the occurrence of ischemic stroke, chronic hypoperfusion in the brain parenchyma, and white-matter lesions in patients with CLAD that were possibly caused by subcortical

ischemia and micro-embolization [14,15]. A meta-analysis in patients with asymptomatic CA stenosis also reported a significant association between poor cognitive performance and hypoperfusion and white-matter lesions as well as age, sex, and education [16]. Although the severity of white-matter lesions is strongly associated with poor cognitive performance [17], atherosclerosis of medullary vessels is invariably found in areas of white-matter lesions, including in our study. These changes in the small arteries are mainly related to ageing and atherosclerotic risk factors [6,18,19]. Patients with CLAD occasionally have these risk factors, and hence they could develop white-matter lesions and cognitive decline. Furthermore, a recent study reported that

CA stenosis exacerbates cerebral hypoperfusion, which may subsequently cause brain atrophy, cognitive decline, and dementia [20]. Although it is well known that strict treatment of atherosclerotic risk factors and intervention for CLAD are important to reduce the occurrence of ischemic stroke, such management might also be necessary to prevent a progressive decline in cognitive performance.

However, it is still unclear why drinking habit contributed to the poor cognitive performance of patients with CLAD. Hippocampal volume was reported to be significantly decreased in chronic alcoholism [21], and a recent report suggested that cortical and subcortical shrinkage was more evident in those with alcohol-use disorders than healthy controls [22]. Dehydration in those with CLAD may increase the hypoperfusion, which might worsen patients' cognition. The fact that none of the MoCA subscores differed between patients who did and did not drink alcohol suggests that the influence of alcohol might be insignificant. This is an inconclusive issue that requires further research.

The analysis of MoCA subscores revealed that attention, memory, and orientation were the common factors significantly associated with age, PVH, and cerebral perfusion. Attention, motivation, and orientation are controlled by the prefrontal-subcortical circuit, which is occasionally affected by ischemic lesions [6]. Frontal hypoperfusion contributes to impaired attention in vascular dementia [23]. Thus, age, PVH, and hypoperfusion might cause frontal lesions, especially in the prefrontal-subcortical circuit, resulting in attention, memory, and orientation impairments. In contrast, circulatory failure and hypoxia frequently occur in patients with multiple atherosclerosis, which might lead to lower hippocampal volumes and the occurrence of Alzheimer's disease [24,25]. We did not assess the patients longitudinally and were unable to determine whether CLAD directly caused the cognitive decline or induced the early stage of Alzheimer disease. Further studies are needed to assess the role of atherosclerosis in cognitive decline and the onset of dementia.

The study was subject to some limitations. First, the number of patients was small. Second, we performed a simple evaluation of cognitive performance rather than using a more complex test battery. A multicenter prospective observational study should be conducted to confirm the results using various batteries. Third, this was a cross-sectional, observational study, and a longitudinal follow-up was not conducted. This may have led to under-diagnosis of cognitive impairment. Finally, although we speculated that patients' impaired cognitive performance was due to frontal hypoperfusion and dysfunction of the prefrontal-subcortical circuit, we could not prove this in this study.

In conclusion, a high percentage of patients with CLAD showed cognitive impairments that were associated with older age, current drinking habit, severe PVH, and cerebral hypoperfusion.

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