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The Impact of Cortical Cerebral Microinfarcts on Functional Outcomes in Patients With Ischemic Stroke

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HIGHLIGHTS

- Cortical cerebral microinfarcts (CMIs) are commonly found in the elderly and stroke patient.
- CMIs affect on poor functional outcome after stroke.
- Even after adjusting for confounders including age, the impact of CMI still remained.

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The authors have no potential conflicts of interest to disclose.

ABSTRACT

The present study examined cortical cerebral microinfarcts (CMIs) on a 3T magnetic resonance imaging and investigated the impact of CMIs on the comprehensive functional outcomes during the post-stroke rehabilitation period. Patients with acute phase of first-ever ischemic stroke were retrospectively recruited (n = 62) and divided into 2 groups with and without CMIs. Clinical parameters including age, sex, stroke lesion laterality, location, the National Institutes of Health Stroke Scale score, as well as history of hypertension, dyslipidemia, diabetes mellitus, and smoking were obtained. Functional outcomes were assessed twice at baseline and one month later with the Korean version of the Mini-Mental State Examination, the Berg balance scale (BBS), and the functional independence measure. Partial correlation and multiple linear regression analyses were used to examine the relationship between the presence of CMIs and the change in functional outcomes. At least one CMI was reported in 27 patients, who were older ($p = 0.043$). The presence of CMIs was significantly associated with functional impairment in all 3 functional outcomes, after controlling for confounding factors ($p < 0.05$). CMIs might contribute to poor functional outcomes during the post-stroke rehabilitation period. These results suggest that CMIs should be considered when establishing rehabilitation treatment strategies or making a prognosis.

Keywords: Stroke; Cerebral Infarction; Functional Outcome; Rehabilitation

INTRODUCTION

Cortical cerebral microinfarcts (CMIs) are small intracortical ischemic lesions that were usually detected by autopsy or neuropathologic examination [1,2]. As the quality of brain imaging improves, CMIs can be found on a 3T or 7T magnetic resonance imaging (MRI). Based on 3T MRI, the prevalence of CMIs ranged from 14.7% to 52.3% in patients with ischemic stroke [3-7].

Cerebral small vessel diseases, microembolism, and hypoperfusion have been suggested as major causes of CMIs in a review [1]. In another large cohort study, possible risk factors of CMIs were age, hypertension, diabetes, dyslipidemia, atrial fibrillation, and other vascular markers such as white matter hyperintensity and cerebral microbleeds [5]. Even when only a few CMIs are identified by naked eye, many more lesions of invisible size may exist. They can

cause perilesional brain atrophy and may disrupt sophisticated neural connections especially concerning executive and visuospatial functions, as well as language processing [4,5,8]. However, the exact underlying mechanism remains unknown.

Previous studies revealed that CMIs are associated with cognitive impairment in elderly with or without dementia or other cerebrovascular diseases [2,9-11], However, despite the common vascular conditions or other risk factors, there are few studies about CMIs in stroke patients. Those limited studies have primarily focused on cognitive outcomes only, but not on motor function or daily activity performance [7,11,12].

To address this gap, the present study aimed to examine CMIs on a 3T MRI in the patients with acute phase of ischemic stroke, and to investigate the impact of CMIs on a comprehensive range of functional outcomes during the post-stroke rehabilitation period.

MATERIALS AND METHODS

Subjects

We retrospectively recruited 62 patients from April 2018 to December 2021 who met the following inclusion criteria: (1) first-ever ischemic stroke; (2) age > 18 years old; (3) had undergone 3T brain MRI within 1 week of hospital admission; (4) admitted to a neurology or neurosurgery unit and transferred to a rehabilitation unit within 6 months of onset. Patients with other neurological comorbidities such as pre-stroke dementia or Parkinson's disease were excluded. Cases of suboptimal imaging quality or contraindication to MRI were also excluded from the analysis. The study protocol was approved by the Institutional Review Board (IRB No.2022-03-005) of the authors' institution, and informed consent was waived due to the retrospective study design.

Methods

Data on demographics and clinical characteristics were obtained from the medical records upon admission. A consensus was reached between neuroradiologist, neurologist, and neurosurgeon regarding the diagnosis, type, location, and laterality of stroke lesions. Initial stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS). The presence of vascular risk factors (i.e., history of hypertension, dyslipidemia, diabetes mellitus, and current smoking) was determined by questionnaires, drug prescriptions, and laboratory tests in line with the previous studies [5,11,12].

Enrolled patients underwent brain MRI at baseline (PHILIPS Ingenia MRI 3T scanner; Philips, Amsterdam, The Netherlands) according to the following sequences: diffusion-weighted imaging, 3-dimensional T1-weighted imaging, T2-weighted imaging, and 3-dimensional fluid attenuated inversion recovery (FLAIR) sequences. Among them, the last 3 sequences were used to identify CMIs. CMIs were defined as intracortical lesions, < 5 mm in diameter, perpendicular to the cortex, hypointense on T1-weighted, and hyperintense or isointense on T2 weighted and FLAIR images (**Fig. 1**) [1,2,4,5,7]. Two experienced observers, unaware of the clinical data, counted CMIs independently and screened out cerebral microbleeds, enlarged perivascular space, blood vessel, lacunar infarct, and white matter hyperintensity according to the neuroimaging standards for research [13]. Lesions within 1cm around the acute large infarct were not considered in this study. In case of disagreement, consensus was reached through discussion. After the completion of all 3 MRI sequences and

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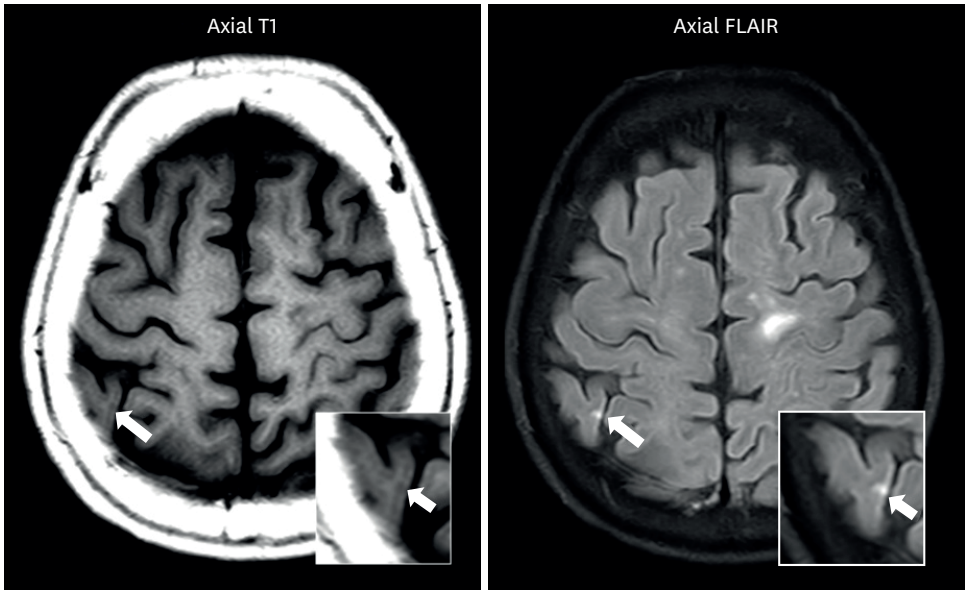

Fig. 1. Example of CMIs on a 3T brain magnetic resonance imaging. The CMIs (arrow) were shown as a hypointense on T1-weighted image and as a hyperintense on FLAIR image.
CMI, cortical cerebral microinfarct; FLAIR, fluid attenuated inversion recovery.

the identification of CMIs, the patients were divided into 2 groups according to the presence of CMI lesion.

All patients completed the 3 following assessment tools twice, at the time they were transferred to a rehabilitation unit (baseline) and 1 month later: the Korean version of the Mini-Mental State Examination (K-MMSE), the Berg balance scale (BBS), and the functional independence measure (FIM) score. The K-MMSE is a screening tool for cognitive impairment. It consists of orientation, memory, attention, calculation, language, and visual construction domains. The total available score is 30 [14]. The BBS is a widely used scale to assess one's ability to maintain balance based on 14 tasks: sitting to standing, standing unsupported, sitting unsupported, standing to sitting, transfers, standing with eye closed, standing with feet together, reaching forward with outstretched arm, retrieving object from floor, turning to look behind, turning 360 degrees, placing the foot alternately on a step, standing with 1 foot in front, and standing on one foot. The total available score is 56 and it helps predict the risk of falls, length of hospitalization, and assistive device dependency for ambulation [15]. The FIM is a measure of motor and cognitive functioning based on 18 items about self-care, sphincter control, mobility, locomotion, communication, and social cognition. The total score ranges from 18 to 126 [16].

Statistical analysis

Two groups with and without CMIs were compared using the χ^2 test or Fisher exact test for categorical variables, and independent t-test for continuous variables. Multiple logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between the vascular risk factors and the presence of CMIs. For the correlations between the change in functional outcomes (i.e., $^{\triangle}$K-MMSE = K-MMSE score at 1 month − K-MMSE score at baseline) and CMIs, partial correlation and multiple linear regression analyses were conducted, adjusting for age, sex, NIHSS score, lesion location, and lesion laterality. Inter-rater reliability in CMI identification was calculated with Cohen κ statistic.

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Statistical analyses were performed using SPSS v18.0 for Windows (SPSS, Chicago, IL, USA) and $p < 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the groups with and without CMIs were compared in **Table 1**. Among 62 patients who had first-ever ischemic stroke and underwent the 3 sequences of brain 3T MRI, 27 patients had one or more CMIs. Patients with CMIs were older (74.7 ± 12.96 vs. 68.22 ± 11.58; $p = 0.043$), but did not differ in sex ($p = 0.177$), days from onset ($p = 0.305$), lesion laterality ($p = 0.244$), lesion location ($p = 0.849$), and the presence of vascular risk factor ($p = 0.879$ for hypertension; $p = 0.874$ for dyslipidemia; $p = 0.535$ for diabetes mellitus; $p = 0.167$ for current smoking).

The functional outcomes at baseline and at 1 month were presented in **Table 2**. There was no baseline difference in the NIHSS score at admission (6.62 ± 5.06 vs. 6.65 ± 4.39; $p = 0.982$), the K-MMSE (18.88 ± 8.43 vs. 20.45 ± 7.61; $p = 0.446$), BBS (21.92 ± 22.97 vs. 21.77 ± 19.21; $p = 0.978$), and FIM score (59.29 ± 28.8 vs. 64.68 ± 19.92; $p = 0.410$) between the 2 groups. Compared to group without CMIs, group with CMIs showed significant changes at 1 month in the K-MMSE (2.0 ± 2.11 vs. 3.37 ± 2.61; $p = 0.03$), BBS (3.62 ± 5.62 vs. 18.82 ± 12.67; $p < 0.001$), and FIM score (9.14 ± 7.95 vs. 22.17 ± 13.72; $p < 0.001$).

In the multiple logistic regression model, none of the risk factors were significantly associated with CMIs (OR, 1.218; 95% CI, 0.386–3.847; $p = 0.737$ for hypertension; OR, 1.287; 95% CI, 0.373–4.445; $p = 0.689$ for dyslipidemia; OR, 0.650; 95% CI, 0.184–2.298; p=0.503 for diabetes mellitus; OR, 0.482; 95% CI, 0.160–1.449; $p = 0.194$ for current smoking). After adjusting for potential confounders including age, sex, and NIHSS score, these findings remained unchanged.

Table 1. Demographic and clinical characteristics of groups with and without CMIs (n = 62)

Variable	With CMIs (n = 27)	Without CMIs (n = 35)	p value
Age (yr)	74.70 ± 12.96	68.22 ± 11.58	0.043*
Sex			0.177
Male	10 (37)	19 (54.3)	
Female	17 (63)	16 (45.7)	
Days from onset	36.48 ± 36.51	27.80 ± 29.56	0.305
Ischemic stroke	27 (100)	35 (100)	
Lesion laterality			0.244
Left	13 (48.1)	18 (51.4)	
Right	14 (51.9)	14 (40.0)	
Bilateral	0	3 (8.6)	
Lesion location			0.849
Anterior cerebral artery	0	0	
Middle cerebral artery	17 (63.0)	20 (57.1)	
Posterior cerebral artery	6 (22.2)	10 (28.6)	
Multiple locations	4 (14.8)	5 (14.3)	
Vascular risk factor			
Hypertension	19 (70.4)	24 (68.6)	0.879
Dyslipidemia	9 (33.3)	11 (31.4)	0.874
Diabetes mellitus	8 (29.6)	13 (37.1)	0.535
Current smoking	7 (25.9)	15 (42.9)	0.167

Values are presented as mean ± standard deviation or number (%).
CMI, cortical cerebral microinfarct.
*$p < 0.05$.

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Table 2. Functional outcomes measured at the 2 time points in groups with and without CMIs

Variable	With CMIs (n = 27)	Without CMIs (n = 35)	p value
NIHSS at admission	6.62 ± 5.06	6.65 ± 4.39	0.982
K-MMSE at baseline	18.88 ± 8.43	20.45 ± 7.61	0.446
K-MMSE at 1 mon	21.18 ± 7.47	23.45 ± 6.55	0.208
△K-MMSE	2.00 ± 2.11	3.37 ± 2.61	0.030*
BBS at baseline	21.92 ± 22.97	21.77 ± 19.21	0.978
BBS at 1 mon	25.11 ± 23.40	40.60 ± 13.10	0.004†
△BBS	3.62 ± 5.62	18.82 ± 12.67	< 0.001†
FIM at baseline	59.29 ± 28.80	64.68 ± 19.92	0.410
FIM at 1 mon	67.70 ± 29.89	86.85 ± 22.54	0.008†
△FIM	9.14 ± 7.95	22.17 ± 13.72	< 0.001†

Values are presented as mean ± standard deviation.
CMI, cortical cerebral microinfarct; NIHSS, National Institutes of Health Stroke Scale; K-MMSE, Korean version of Mini-Mental State Examination; BBS, Berg balance scale; FIM, functional independence measure.
*p < 0.05, †p < 0.01.

Table 3. Partial correlation and multiple linear regression analyses: associations between the presence of cortical cerebral microinfarcts and the changes in functional outcomes

Variable	Partial correlation		Multiple linear regression	
	r	p value	β	p value
△K-MMSE	−0.266	0.045*	−0.206	0.038*
△BBS	−0.605	< 0.001†	−0.467	< 0.001†
△FIM	−0.450	< 0.001†	−0.255	0.023*

Adjusted for age, sex, National Institutes of Health Stroke Scale score, lesion location, and lesion laterality.
K-MMSE, Korean version of Mini-Mental State Examination; BBS, Berg balance scale; FIM, functional independence measure; r, partial correlation coefficient; β, standardized beta coefficient.
*p < 0.05, †p < 0.01.

In partial correlation and multiple linear regression analyses, the presence of CMIs was significantly associated with the changes in all 3 functional outcomes at the time of transfer to the rehabilitation unit and after 1 month (i.e., △K-MMSE, △BBS, and △FIM). This result remained consistent after controlling for age, sex, NIHSS score, lesion location, and lesion laterality (**Table 3**). The BBS score showed the strongest association with the presence of CMIs (β = −0.467; p < 0.001). Scores on the K-MMSE and the FIM were also significantly associated with the presence of CMIs (β = −0.206; p = 0.038 for K-MMSE; β = −0.255; p = 0.023 for FIM). Inter-rater reliability in CMI identification was κ = 0.81 (p < 0.05).

DISCUSSION

The present study demonstrated that CMIs might contribute to the compromised functional outcomes during the rehabilitation period in patients with ischemic stroke. Cognitive decline in people with CMIs has been previously reported, but this study showed that it may also affect a broad spectrum of functioning in terms of balance, postural stability, ambulatory function, and ability to perform daily activities.

The mechanism of CMIs has not been clearly elucidated. Although being limited, several findings offer clues to the potential mechanism of how CMIs can affect functional outcomes. Histologically, microinfarcts show cystic, glial changes, or inflammatory response, and neuronal loss including axonal damage occurs in adjacent tissues. It also alters sensitivity to protease involved in apoptosis, making brain tissues more susceptible to ischemic injury and all of these processes can jointly disrupt neural connection [17]. Neuronal death and blood-brain barrier breakdown ultimately contributed to overall cortical atrophy [8].

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An animal model study by Summers et al. [18] reported that neural activities were significantly reduced in the areas that were of 12-times larger volume than that of the microinfarct core. Also, a blockade of motor output occurred due to damaged cortical and subcortical circuit. Additionally, even the white matter tracts of the remote brain region connected to CMIs were affected and the communication between local and remote brain areas via white matter pathways became difficult [19].

CMIs are commonly found in the frontal and parietal cortex. The cognitive domains primarily affected by CMIs are visuospatial function, verbal and visual memory, executive function, and processing speed, which are also important for gross motor function and performance in daily activities [2,5,11,12]. Reorganization and plasticity are pivotal in the post-stroke period, and the microvascular burden such as CMIs may decrease the efficiency and connectivity of the spared brain regions and negatively affect functional outcomes [20].

Thus far, research has disproportionately focused on cognitive outcomes of CMIs because they concern the cortical areas of the brain. However, the cortex is not only pertinent to cognitive domain, but also to other domains including movement, sensation, and language. Therefore, CMIs can affect a broad spectrum of functional outcomes above and beyond cognitive ability. This view is bolstered by the present study's finding that CMIs are not only significantly associated with the K-MMSE score, but also with the BBS and the FIM scores. The effect sizes of the relationships were compatible.

The size of CMIs varies from 50 μm to 5 mm and can be detected differently depending on the resolution of the MRI. In the 3T MRI used in this study, most CMIs are 2–3 mm [4]. Even when only a few CMIs are observed by naked eye, there are more actual lesions of invisible size [5]. Therefore, few studies have addressed a linear association between the number or size of the CMIs and functional decline. A prospective memory clinic study suggested that patients with > 2 CMIs had greater cognitive decline than patients with ≤ 2 CMIs [2]. As mentioned above, so far, it is difficult to reflect the actual number and size of CMIs accurately. Further studies with higher resolution of MRI are needed to identify these linear relationships.

CMIs were observed in 43% of the subjects and it was within the range of the prevalence statistics from previous studies. In fact, the reported prevalence statistics are notably heterogeneous and the following causes are suggested: (1) MRI has only been recently used while most of the studies on CMIs were based on autopsy and the sample sizes were small [1,2]. (2) Microscope and paraffin sections were used for histopathological studies and the reference diameters varied from 50 μm to 5 mm before a consensus was reached [21]. (3) The inclusion criteria for each study were different. (4) As the resolution of MRI has significantly improved, previously undetected lesions have become increasingly more identifiable.

When clinical characteristics were compared, subjects with CMIs were older. Microinfarcts are very common in elderly, and CMIs were found in 33% of the elderly sample of Sonnen et al. [22] who had normal cognitive function. The main mechanisms of CMIs might be also age-related; cerebral small vessel disease, microembolism, and decreased cerebral perfusion [23]. Age itself can be a significant predictor of good functional outcome after stroke [24]. However, we adjusted for confounders including age when partial correlation and multiple linear regression analyses were conducted and there was no difference in the NIHSS score at admission, the K-MMSE, BBS, and FIM score at baseline between the 2 groups. Therefore, it is unlikely that differences due to age affected the results.

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Various risk factors related to CMIs have been reported. In one study on memory clinic patients, history of hyperlipidemia, stroke, and cardiovascular disease were associated with CMIs, while smoking, hypertension, and diabetes mellitus were not [4]. Being male, current smoking, history of heart disease, and history of stroke were related to CMIs in another population-based prospective cohort study [25]. An additional study found that CMIs were only associated with previous stroke but not with any other vascular risk factors [26].

In the present study, ORs for vascular risk factors contributing to CMIs were computed. Among the 4 vascular risk factors (i.e., hypertension, dyslipidemia, diabetes mellitus, and current smoking), none was significantly associated with the CMIs. Shown in **Table 1**, this may be because there was little difference in risk factors between the 2 groups, except for the presence of CMI. The results of previous studies to identify the risk factors for CMIs were all heterogeneous depending on the study settings.

Smoking is a widely known risk factor for ischemic stroke. It accelerates the development of atherosclerosis, which can interfere with oxygen and blood supply to tissues [27]. The exposure to smoking induces platelet aggregation, impaired fibrinolysis, slow blood flow, and vasoconstriction contributing to lacunar infarct [28]. In a meta-analysis, a dose-dependent relationship between smoking and the risk of stroke was found. Smoking 5 more cigarettes per day increased the risk of stroke by 12% [29]. Further studies with larger sample sizes are needed to verify a clear contribution of smoking to CMIs.

In the current study, all subjects were ischemic stroke patients and previous stroke history was excluded from the vascular risk factor analysis by study design. Diabetes mellitus can play an important role in vascular disease. However, if blood sugar is under proper control, it does not necessarily increase the risk of cerebral microvascular lesions [30]. The cortical watershed areas are where microinfarcts are often found, and a decrease in cerebral perfusion leads to CMIs, as previously mentioned [31]. So, low blood pressure, rather than high blood pressure, is likely to be one of the contributing factors to CMIs.

Hilal et al. [32] revealed the associations between cardiac biomarkers and cardiac disease with CMIs. Hypertension was a common trend in the CMI group but was not an independent risk factor of CMIs. Higher level of N-terminal pro-brain natriuretic peptide, atrial fibrillation, ischemic heart disease, and congestive heart failure were significantly associated with CMIs. Future studies need to focus on these clinical data.

The present study is the first one verifying the relationship between CMIs and a comprehensive range of functional outcomes in stroke patients, but there are some limitations. First, the subjects were patients with ischemic stroke only and the study findings' generalizability is limited. To enhance the generalizability, large scale comparative studies including hemorrhagic lesions would be promising. Second, it was not possible to calculate the volume of primary infarct. Instead, we used data on lesion location, laterality, and the NIHSS score to indirectly correct for the effect of a primary infarct on the functional outcomes. In several studies, NIHSS score was significantly correlated with the volume of an infarct based on quantitative analyses of brain MRI such as diffusion-weighted and perfusion-weighted imaging in acute ischemic stroke. Contrary to popular belief, a larger infarct volume was not always associated with worsened clinical symptoms, and even a small subcortical infarct was associated with serious symptoms [33,34]. Therefore, the NIHSS score might be more suitable for the evaluation of functional outcomes than the volume of infarct.

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CONCLUSION

CMIs might contribute to poor functional outcomes during the post-stroke rehabilitation period. In this study, it was shown that CMIs can affect a broad spectrum of functional outcomes encompassing cognitive functions, gross motor functions, and performance in daily activities. These results suggest that CMIs should be considered when establishing rehabilitation treatment strategies or making a prognosis.

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