



Is the Location of White Matter Lesions Important in the Swallowing Function of Older Patients with Mild Stroke?

Hyun Im Moon¹ · Gyu Seong Kim¹ · Eunchoe Lee¹

Received: 4 April 2018 / Accepted: 20 October 2018 / Published online: 31 October 2018
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Abstract

Older patients with stroke have poor functional prognosis compared to younger patients. Patients with stroke who have severe white matter (WM) lesions have been reported to have swallowing problems. The aim of this study was to determine whether the location of WM lesions affects swallowing function in older patients with mild stroke. We conducted a retrospective analysis of 88 patients aged > 65 years who had a National Institutes of Health Stroke Scale score of ≤ 5 and who underwent videofluoroscopic swallowing examination after their first stroke. Participants were divided into three groups according to the involvement of corticobulbar tract (CBT) as follows: group I, no involvement of CBT; group II, involvement of CBT in one hemisphere; and group III, involvement of CBT in both hemispheres. Linear regression analysis showed that pharyngeal transit time tended to increase according to the involvement of CBT in WM lesion ($p = 0.043$). In addition, inadequate laryngeal elevation was related to the involvement of CBT ($p = 0.016$). Early spillage, inadequate laryngeal elevation, and penetration could also be predicted by Fazekas grade. Accordingly, the location of WM lesions can be regarded as a potential predictive factor for dysphagia. Moreover, in patients with WM lesions involving CBT, detailed evaluation of dysphagia is required.

Keywords Deglutition · Stroke · White matter · Periventricular leukomalacia · Prognosis · Corticobulbar tract

Introduction

Older patients with stroke have a poor functional prognosis compared to younger patients [1]. Initial stroke severity is directly associated with functional outcome and is considered to be a strong prognostic factor [2]. However, some elderly patients with stroke have a relatively poor prognosis even though their neurologic sequelae are mild and they do not exhibit any complications. In recent decades, patients with stroke who have severe white matter (WM) lesions have been reported to have a poor functional prognosis [3]. White matter lesions, also known as leukoaraiosis, can be detected as abnormal hypointensities on computed tomography scans and as hyperintensities on T2-weighted or fluid-attenuated inversion recovery

magnetic resonance imaging (MRI). A recent LADIS (leukoaraiosis and disability) study with 3-year follow-up results showed that age-related changes in WM independently and strongly predict a rapid global functional decline [4]. A WM lesion appears as a hyperintense lesion in the cerebral WM of T2-weighted MRI. Regions of periventricular hyperintensity in the brain MRI are thought to reflect a decreased amount of nerve fibers. A previous study comparing postmortem brain MRI scans with anatomic findings reported decreased myelin, axons, and oligodendrocytes, but increased microglia in cerebral WM lesions [5]. WM lesions have also been suggested to be a form of end-organ damage [6] caused by a diffuse decrease in cerebral blood flow, suggesting poor cerebral blood flow [7]. Therefore, WM lesions might indicate increased vulnerability to ischemic challenges, such as stroke. In review of cerebral aging, WM lesion as a quantifiable nondisease-related aging of the cerebral WM observed in brain MRI may contribute to a disconnection state. Further, the prefrontal WM was most susceptible to the influence of age,

✉ Hyun Im Moon
feellove99@gmail.com

¹ Department of Rehabilitation Medicine, Bundang Jesaeng General Hospital, 20, Seohyeon-ro 180 beon-gil, Bundang-gu, Seoungnam-si, Gyeonggi-do 13590, Republic of Korea

and it may be associated with performance decline in cognitive domains [8].

A few studies have investigated the influence of WM lesions on swallowing dysfunction. One study reported that unidentified bright objects on MRI had a demonstrable effect on the duration of oropharyngeal swallowing in normal individuals [9]. Also, another previous study suggested that WM connections were clinically important as related to dysphagia in acute purely subcortical stroke patients [10]. In a recent study, WM lesions observed in brain magnetic resonance imaging scans can impart swallowing problems in older patients with mild stroke, regardless of initial stroke severity or other factors associated with lesion location, especially causing oral transit time delay or penetration [11].

Swallowing is a complex process of sensation and movement controlled by the brain. This process involves multiple nervous tissues including the cerebral cortex, the subcortical white matter tract, and the infratentorium [12]. The corticobulbar tract (CBT) plays some role in swallowing. The CBT is known to originate from the primary motor cortex and descend through the corona radiata and internal capsule into the cerebral peduncles. The CBT then innervates the motor cranial nerve nuclei in the brain stem to control the muscles of the face, head, and neck [13]. A previous study reported that involvement of the CBT might be a possible cause of dysphagia in normal pressure hydrocephalus [14].

Recently, there is growing evidence suggesting that clinical significance can be indicated by the anatomic location of white matter lesions and whether the functional integrity of specific fiber bundles is affected. WM lesions at the frontal horns, the so-called “capping,” are in close proximity to cholinergic axons that originate in the basal forebrain. Therefore, these lesions may result in more significant cortical deafferentation because of the more proximal axonal disruption [15, 16]. Another study reported strategic subcortical hyperintensities in cholinergic pathways and executive function decline in Alzheimer patients [17]. These findings might suggest that not only the severity of WM lesions but also the location of the WM lesions has clinical significance associated with neurologic deficit. To our knowledge, there are few studies on the involvement of CBT in WM lesions and dysphagia.

We hypothesized that oropharyngeal dysphagia in older stroke patients with only mild neurologic symptoms is associated with the location of preexisting WM lesions and depends heavily on CBT involvement. The aim of the present study was to test the hypothesis that the involvement of CBT in WM lesions negatively impacts swallowing function in older patients with relatively mild stroke.

Materials and Methods

Participants

Acute and subacute patients with stroke who underwent VFSS in the Department of Physical Medicine and Rehabilitation between January 2012 and November 2017 were included in this study. VFSS was performed to screen for dysphagia. Diagnosis of stroke was limited to cases in which ischemic cerebral infarction had been verified by magnetic resonance imaging (MRI). We included patients aged ≥ 65 years and who had mild stroke and transient ischemic accident (TIA) (score ≤ 5 on the Korean version of the National Institutes of Health Stroke Scale, K-NIHSS) [18]. The exclusion criteria were as follows: (1) missing medical records or brain MRI scans, (2) difficulty identifying the lesion focus, as in subarachnoid hemorrhage, (3) previous history of stroke, dementia, or other diseases that could cause dysphagia, and (4) duration between stroke onset and VFSS evaluation exceeded 30 days. A total of 88 patients satisfied the criteria and were chosen for analysis; data from these patients were collected retrospectively. The study protocol was approved by the institutional review board of our institution, and the requirement for informed consent was waived due to the retrospective design of the study.

Methods

Review of medical records: The medical records and test results of the patients were reviewed retrospectively. Patient demographic and clinical characteristics were recorded, including age, sex, brain lesion laterality (left or right), duration between onset of stroke and VFSS evaluation (number of days), and initial severity of stroke as assessed by the K-NIHSS.

Videofluoroscopic swallowing study: Physicians of the Department of Rehabilitation Medicine conducted the VFSS by following a modified version of Logemann's procedure [19]. Briefly, individuals were seated, and fluoroscopy was performed as the patients swallowed barium mixed with juice, yogurt, thick gruel, or rice. For juice and yogurt, two different volumes were used (2 and 5 ml). Each food type was mixed with undiluted liquid barium to ensure proper bolus observation during the fluoroscopy procedure.

Interpretation of VFSS: In the oral phase, functions such as lip sealing, bolus formation, mastication, early spillage, oral remnants, and oral transit time of the bolus were assessed. In the pharyngeal phase, laryngeal elevation and aspiration/penetration of the respiratory tract were assessed. Moreover, the pharyngeal transit time of the bolus and

swallowing response time until the swallowing reflex was initiated were both recorded. Each individual finding was assessed based on the presence or absence of an abnormal finding. Oral transit time, swallowing response time, and pharyngeal transit times were recorded in seconds. Oral transit time was the interval between the first frame showing tongue tip elevation and the first frame showing arrival of the head of the bolus at the ramus of the mandible. Swallowing response time was the interval between the arrival of the bolus at the ramus of the mandible and the first frame showing upward excursion of the larynx. The pharyngeal transit time was the interval between the end of the oral transit time and the last frame showing the tail of the bolus passing through the upper esophageal sphincter. When the food entered the respiratory tract, but did not pass into the true vocal fold, it was recorded as penetration, whereas when the food passed into the true vocal fold, it was determined to be aspiration.

WM Lesions

Brain MRI scans were evaluated by a physician who was blinded to the patient's clinical symptoms. The severity of WM lesions was determined using fluid-attenuated inversion recovery (FLAIR) magnetic resonance images. Acute infarction and WM lesions were differentiated by comparing diffusion-weighted images and FLAIR images. Severity was rated based on the Fazekas scale, which categorizes WM lesions. Periventricular hyperintensity (PVH) was graded as 0 = absence, 1 = "caps" or pencil-thin lining, 2 = smooth "halo," and 3 = irregular periventricular hyperintensity extending into the deep white matter. Separate deep white matter hyperintense signals (DWH) were rated as 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, and 3 = large confluent areas [20]. Also, the involvement of CBT was determined by two trained researchers depending on the change of signal intensity at the location of CBT, almost halfway between the most anterior and the most posterior points of the lateral ventricle, almost one third between the midline and the most lateral point of the brain, and anterior and medial compared with the corticospinal tract [21]. Participants were divided into three groups according to CBT involvement as follows: group I, no involvement of CBT; group II, involvement of CBT in one hemisphere; and group III, involvement of CBT in both hemispheres (Fig. 1).

Statistical Analysis

Differences between the three groups were evaluated using the Kruskal–Wallis test. Partial correlation analyses with adjustments for age, NIHSS, and Fazekas grade were

performed to examine the correlations between involvement of CBT and swallowing parameters in VFSS. To assess whether clinical characteristics of lesion location, laterality, sex, age, severity of stroke, WM lesion severity, and CBT involvement were independent variables in predicting swallowing problems, while controlling for other possible confounding variables, the corresponding rates of findings were calculated. We set each VFSS finding as an independent variable and determined the corresponding rate of each finding. The 95% confidence intervals and equivalent p values were calculated using multivariate linear logistic regression analysis.

The statistical package SPSS (IBM SPSS Statistics for Windows, Version 21.0; IBM, Armonk, NY, USA) was used for all statistical analyses. Statistical significance was defined as $p < 0.05$.

Results

General Characteristics of the Participants

The demographic and clinical characteristics of the 88 patients are shown in Table 1. Groups according to the location of the WM lesion were as follows: group I (no involvement of CBT) was 45 patients, while group II (involvement of CBT in one hemisphere) and group III (involvement of CBT in both hemispheres) contained 25 and 18 patients, respectively.

Differences Among the Groups According to the Involvement of CBT in WM Lesion

Significant differences were observed in the Fazekas grade (PVH), Fazekas grade (DWH), sum score of Fazekas grade, and the laryngeal elevation abnormality among three groups according to the CBT involvement (Fig. 2).

The relationships between WM lesion's involvement of CBT and VFSS findings are shown in Table 2. The partial correlation coefficients adjusted for age, initial severity (K-NIHSS), and Fazekas sum score were calculated. Statistically significant correlations were observed between the involvement of CBT and delayed pharyngeal transit time and inadequate laryngeal elevation. In the correlation analysis with combined group II + III, it showed similar results: there were significant correlations between the involvement of CBT and delayed pharyngeal transit time, delayed swallowing response time, and inadequate laryngeal elevation. (detailed data were not described.)

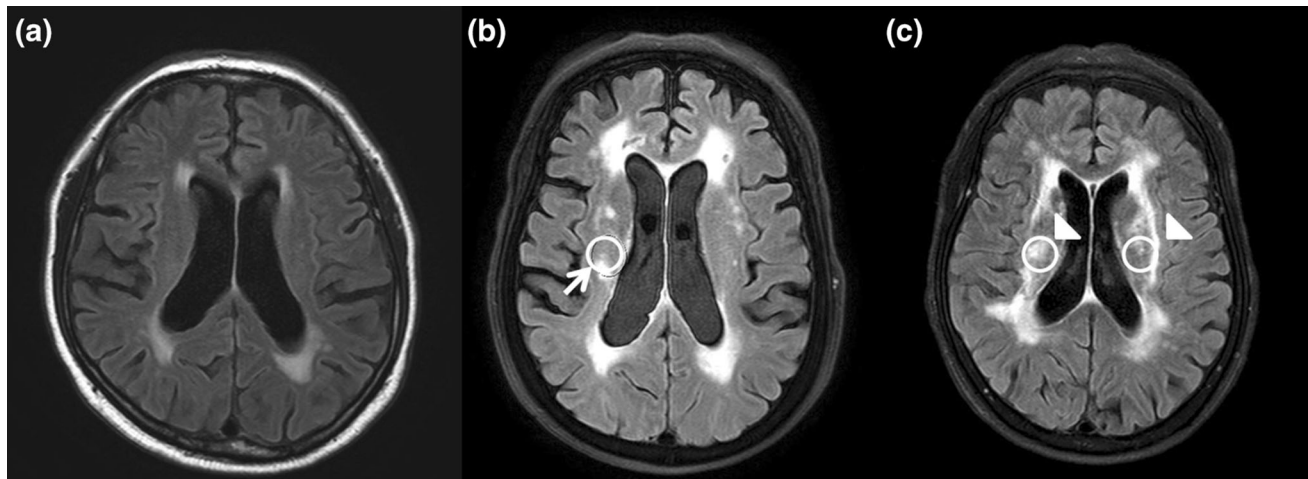


Fig. 1 Fluid-Attenuated Inversion Recovery (FLAIR) image of a brain MRI showing **a** no involvement of the corticobulbar tract (CBT) in white matter lesion, **b** CBT involvement of one hemisphere (white arrow), and **c** CBT involvement of bilateral hemispheres (white arrowheads)

Predictors of Dysphagia

To control for other confounding factors of age, sex, lesion laterality, lesion location, and initial stroke severity, Fazekas grade, multiple logistic regression analyses were conducted to examine the role of WM lesions location in swallowing problems in older patients with mild stroke. Based on the VFSS results, the factors relevant to dysphagia are described in Table 3. Several swallowing parameters were related to the degree of WM lesion severity and involvement of CBT. Early spillage, inadequate laryngeal elevation, and penetration were seen more frequently as Fazekas grade increased ($p = 0.043$, 0.040 , and 0.020 , respectively). In the pharyngeal phase of swallowing, multivariate regression analysis revealed that a WM lesion involving CBT was a significant factor associated with inadequate laryngeal elevation and delayed pharyngeal transit time. Therefore, involvement of CBT by a WM lesion was an independent prognostic factor of pharyngeal swallowing problem, regardless of Fazekas grade.

Discussion

The present study demonstrates that some swallowing parameters after stroke in elderly patients with mild neurologic symptoms are influenced by the severity and location of WM lesions. Moreover, these effects are independent of age, sex, initial stroke severity, lesion location, and lesion laterality. The results, using a linear regression model, indicate that the degree of WM lesions is correlated with the early spillage, laryngeal elevation, and penetration. Also, the location of WM lesion (involvement of

CBT) has some influence on the laryngeal elevation and pharyngeal transit time.

A number of previous studies reported prognostic factors of dysphagia in stroke patients, and the initial severity of the stroke was a strong predictor [22]. However, among patients with mild stroke, NIHSS score was not associated with any of the swallowing parameters according to linear regression analysis. This finding suggests that the K-NIHSS scoring system might not be useful for predicting swallowing problems in older patients with mild stroke.

Considering all previous reports, WM lesions can lead to functional decline in elderly patients, and it may have some important role for presbyphagia often manifested in old age. In a previous study, severe WM lesion was associated with pseudobulbar signs, [23] and WM lesions observed in brain magnetic resonance imaging scans can indicate swallowing problems in older patients with mild stroke, regardless of initial stroke severity or other factors associated with lesion location, especially causing oral transit time delay or penetration [11]. Also, a severe WM lesion might predict stroke-associated pneumonia in patients with acute ischemic stroke [24]. However, in these studies, the location of WM lesions was not considered.

Recently, growing evidences about the location of WM and neurologic deficit were reported. WM lesions at the frontal horns were reported to result in more significant cortical deafferentation and cognitive dysfunction [15, 16]. Another study reported the strategic subcortical hyperintensities in cholinergic pathways and executive function decline in Alzheimer patients [17]. In this study, CBT involvement of WM lesions did affect some parameters of VFSS. Of course, the more severe a WM lesion is, the greater the involvement of CBT. In group comparisons according to CBT involvement, the Fazekas grade showed significant difference among groups. However,

Table 1 Characteristics of older patients with stroke

Characteristics	
Age, years (range)	76.94 ± 7.30 (65–97)
Sex, <i>n</i> (%)	
Male	41 (46.6)
Lesion side, <i>n</i>	
Right/left/bilateral	38/42/6
Lesion location, <i>n</i>	
Supratentorium/Infratentorium	61/25
NIHSS (range)	2.70 ± 1.49 (0–5)
Interval between onset of stroke and VFSS, days	9.75 ± 7.90
Comorbidities, <i>n</i> (%)	
Hypertension	58 (65.9)
Diabetes	26 (29.5)
Dyslipidemia	12 (13.6)
Heart disease	15 (17.0)
Atrial fibrillation	11 (12.5)
Chronic kidney disease	3 (3.4)
Fazekas grade (PVH), <i>n</i> (%)	
Grade 0	9 (10.2)
Grade 1	30 (34.1)
Grade 2	26 (29.5)
Grade 3	23 (26.1)
Fazekas grade (DWH), <i>n</i> (%)	
Grade 0	35 (39.8)
Grade 1	34 (38.6)
Grade 2	17 (19.3)
Grade 3	2 (2.3)
Sum score of Fazekas grade	
0	5 (5.7)
1	23 (26.1)
2	19 (21.6)
3	15 (17.0)
4	13 (14.8)
5	11 (12.5)
6	2 (2.3)
CBT involvement	
Absent/unilateral/bilateral	45/25/18
Current feeding status, <i>n</i> (%)	
Regular diet	17 (19.3)
Soft diet	48 (54.5)
Nasogastric tube	21 (23.9)
None per oral	2 (2.3)

N = 88. Values are presented as mean (± SD) or number of subjects (percentage)

K-NIHSS Korean version of the National Institutes of Health Stroke Scale, *VFSS* videofluoroscopic swallowing study, *PVH* paraventricular hyperintensity, *DWH* deep white matter hyperintensity, *CBT* corticobulbar tract

Multivariate regression analysis showed that the location of CBT had significant influence on the inadequate laryngeal

elevation and prolonged pharyngeal transit time regardless of the Fazekas sum score.

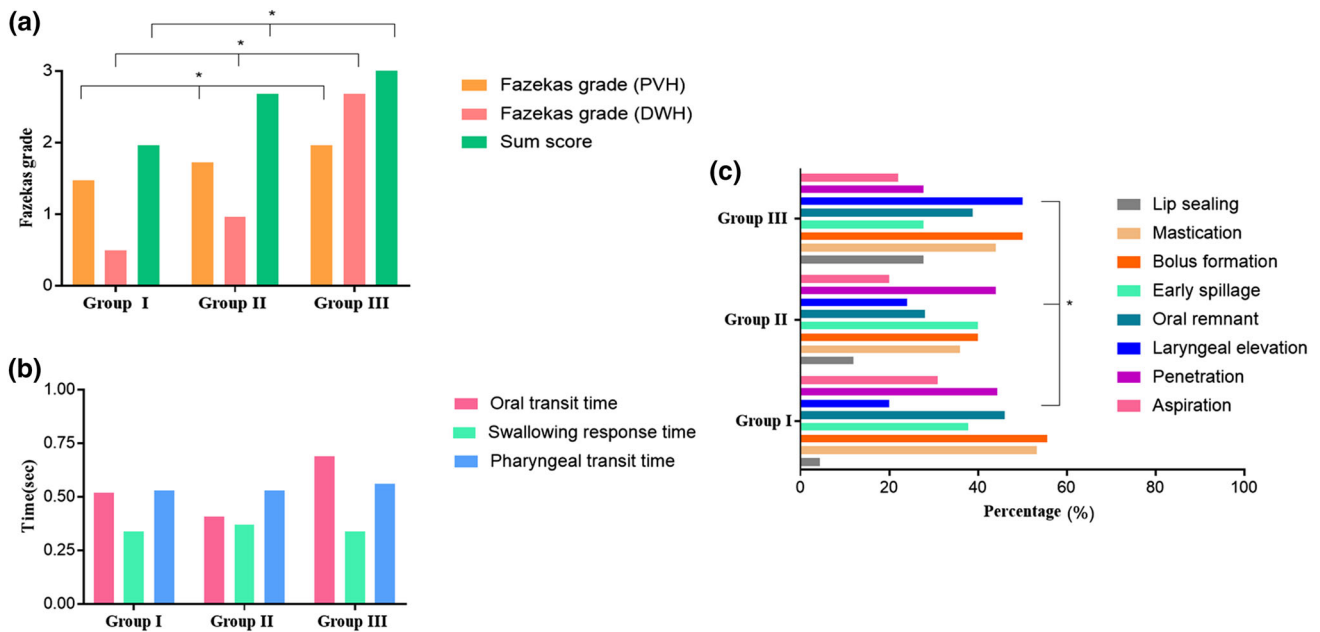


Fig. 2 Characteristics of three groups according to involvement of corticobulbar tract in white matter lesion. **a** Fazekas grade, **b** time measurement of VFSS findings, **c** percentage of abnormal VFSS findings

Table 2 Partial correlation coefficients between CBT involvement and VFSS findings

VFSS findings	Correlation coefficient
Lip sealing	0.200, <i>p</i> = 0.065
Mastication	0.121, <i>p</i> = 0.265
Bolus formation	0.173, <i>p</i> = 0.111
Oral transit time	0.022, <i>p</i> = 0.838
Early spillage	0.021, <i>p</i> = 0.851
Oral remnant	0.013, <i>p</i> = 0.909
Swallowing response time	0.164, <i>p</i> = 0.223
Pharyngeal transit time	0.206, <i>p</i> = 0.047*
Laryngeal elevation	0.282, <i>p</i> = 0.008*
Penetration	0.040, <i>p</i> = 0.716
Aspiration	0.084, <i>p</i> = 0.443

Values are adjusted for the age, NIHSS, Fazeka sum score

**p* < 0.05

Therefore, abnormal swallowing parameters or prolonged pharyngeal transit times might result from the combined effects of acute focal damage and preexisting destruction of CBT pathways. Increased periventricular WM lesions might contribute to this inefficient use of neural networks. This observation might be due to disruptions in the corticobulbar tract [25].

In swallowing function after stroke, CBT might have an important role. It plays a functional role in motor function of the non-oculomotor cranial nerve, therefore it affects the

Table 3 Factors affecting VFSS findings: multivariate prediction models using logistic regression analysis

VFSS parameters	OR	95% CI	<i>p</i> value
Early spillage			
Fazeka sum score	4.112	1.012–2.054	0.043
Laryngeal elevation			
Fazeka sum score	4.237	0.351–0.975	0.040
CBT involvement	3.951	1.294–12.064	0.016
Pharyngeal transit time			
CBT involvement	1.962	0.037–0.176	0.043
Penetration			
Fazeka sum score	1.533	1.068–2.201	0.020

OR odds ratio, CI confidence interval, CBT corticobulbar tract

bulbar function. The CBT is associated with the muscles of the face, head, and neck. For this reason, injury of CBT often results in bulbar symptoms, such as dysphagia, dysarthria, and facial palsy [26]. A recent study reported that early swallowing recovery after stroke was influenced by lesions disrupting CBT fibers. Disrupting these fibers would lead to disconnection of the swallowing centers in the cortex and brain stem [27].

Based on these previous studies mentioned above, WM lesion location involving CBT might affect the integrity of the tract that results in dysphasia after stroke. The involved tract holds primary influence on the pharyngeal phase on swallowing, inadequate laryngeal elevation, and delayed

pharyngeal transit time. In a previous study, more severe WM lesions showed longer oral transit times [11]. However, in this study, the location of CBT affected the pharyngeal phase predominantly.

The main limitations of our study are its retrospective design and the relatively small sample size. However, although imaging was assessed retrospectively, videofluoroscopic swallowing evaluations were performed according to a standard method. Moreover, clinical data such as vascular risk factors are routinely collected in patient admission records. Another limitation relates to the imaging analysis method. In our study, we assessed the involvement of CBT in WM lesions by only the presence of high signal intensity in structural MRI. The integrity of CBT was not demonstrated by a more objective method, such as diffusion tensor tractography.

Further research with a prospective design and advanced neuroimaging analysis such as diffusion tensor imaging is needed to confirm the associations of swallowing problems with WM lesion location and to complement the limitations of this study. Also, we could not analyze all the region of interests related with swallowing function except CBT. In future study, another ROI associated with swallowing function should be considered to complement our study.

Conclusions

In summary, our results suggest that WM lesion's location involving the CBT might affect the integrity of the tract that results in dysphagia in older patients with mild stroke, regardless of the initial stroke severity. CBT predominantly influenced the pharyngeal phase of swallowing, with inadequate laryngeal elevation and delayed pharyngeal transit time. Accordingly, the location of WM lesions can be regarded as a potential predictive factor for dysphagia. Moreover, in patients with WM lesions involving CBT, a detailed evaluation for dysphagia is needed.

Compliance with Ethical Standards

Conflict of interest The authors have no potential conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

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Hyun Im Moon MD

Gyu Seong Kim MD

Eunchae Lee MD