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Voxel-based Lesion-symptom Mapping of Post-stroke Cricopharyngeal Dysfunction

Jun Yup Kim[1,2*], Jong Mi Park[1,2], Yong Wook Kim[1,2†]

Yonsei University College of Medicine, Department and Research Institute of Rehabilitation Medicine[1], Yonsei University College of Medicine, Research Institute of Rehabilitation Medicine[2]

Introduction

Stroke commonly leads to swallowing disorders and among the post-stroke swallowing disorders, cricopharyngeal dysfunction (CPD) has been reported to occur in 50% of brainstem strokes. However, even in the supratentorial post-stroke patients, CPD occurs not rarely, and the neuroanatomical location for CPD is still not elucidated. For these reasons, we aimed to analyze the relationship between development of CPD and lesion location in post-stroke patients through this retrospective case-control study.

Methods

Post-stroke CPD was diagnosed when the residue was more than 25% of the pyriform sinus after swallowing. Medical records and Video Fluoroscopic Swallowing Studies (VFSS) of first-ever stroke patients who were admitted to our hospital from 2009 to 2019 were reviewed. We classified 50 patients with post-stroke CPD as the experimental group and 69 patients without CPD as the control group. Regions of interest were drawn manually on T1-weighted magnetic resonance images using 3d-slicer software, and data were normalized to a standard brain template in order to examine the neural correlates of CPD using voxel-based lesion-symptom mapping (VLSM) analysis. Only for the diagnosis of CPD, dichotomous scores were entered into VLSM analysis and the Liebermeister statistics were estimated. The relationship between brain lesion and the ratio of post-swallow remnant to the total area of the pyriform sinus (rPSR) was tested using generalized linear model. After then, we performed adjusted lesion symptom mapping using the Freedman-Lane multivariable regression approach to model rPSR controlling for age and total lesion volume because these factors have previously been shown to impact swallow physiology or stroke outcome in general. For all tests, we used a P-threshold of 0.01 corrected for multiple comparisons with permutation thresholding (5000 permutations).

Results

Analyses using voxel-wise subtraction and the Liebermeister statistics indicated that lesions of globus pallidus, and middle & inferior frontal lobes in the right cerebral

hemisphere were associated with development of CPD (Pcorrected = 0.01, Table 2, Figure 1). After adjustment of age and total lesion volume, which are already known as possible effectors for the development of dysphagia, statistically significant correlations were found between rPSR and lesions of the right rectal gyrus and globus pallidus, the left middle frontal lobes, the right orbital gyrus and medial frontal lobes (Pcorrected = 0.01, Table 3, Figure 2).

Conclusion

Our results suggest that damages to the globus pallidus and frontal lobes in the bilateral cerebral hemisphere is associated with increased amount of post-swallow remnant in the pyriform sinus which implies the impaired relaxation of cricophayngeus muscle. Future researches are needed to develop a neuroanatomical model of post-stroke CPD

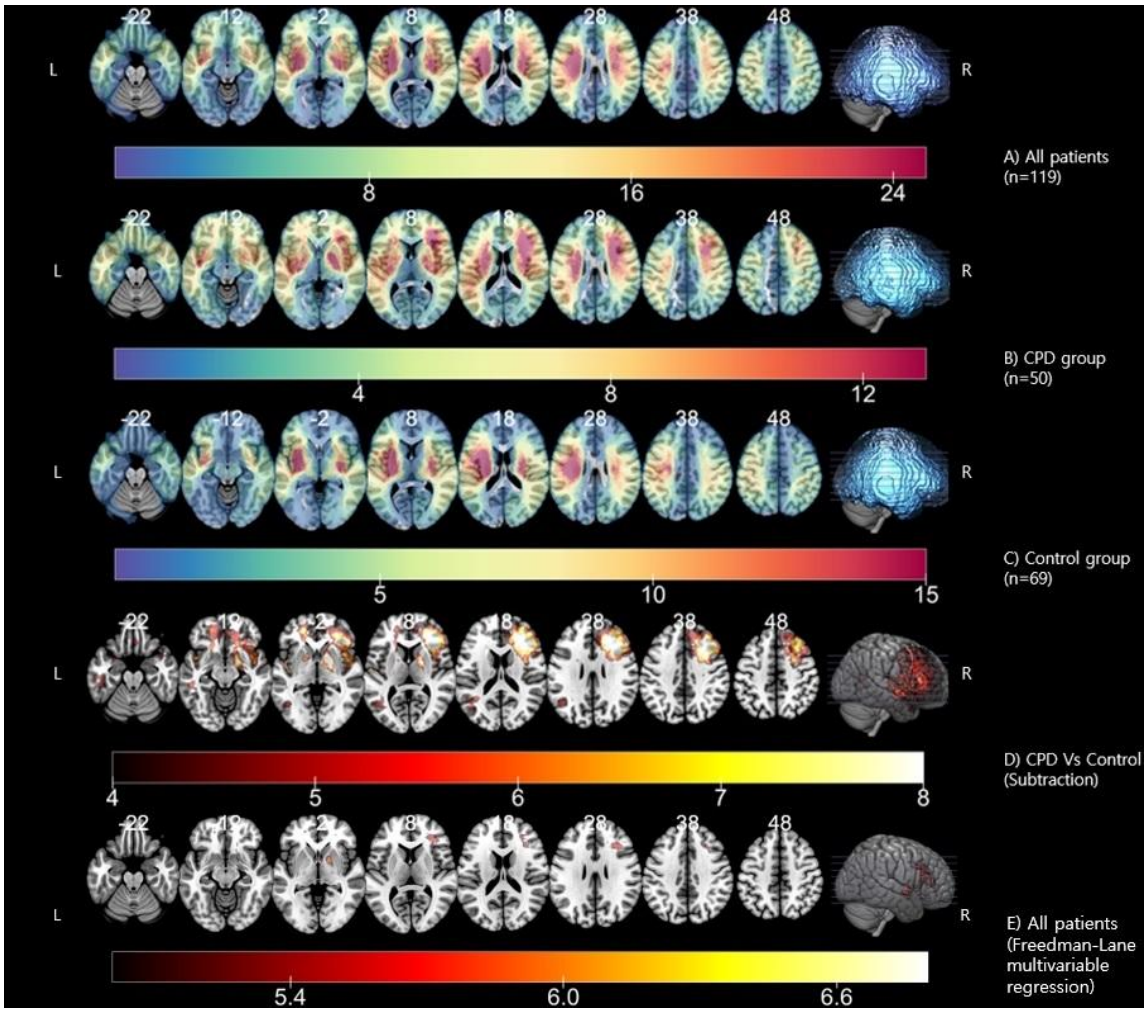

Fig. 1 From top to bottom, A) overlay lesion plots for all patients, B) CPD group, C) control group, D) CPD group overlay subtracted with control group overlay, and E) Voxel-based lesion-symptom maps showing lesioned areas significantly associated with ratio of post-swallow remnant to the total area of the pyriform sinus (rPSR) after controlling for age and total lesion volume (P-threshold of 0.01 corrected for multiple comparisons with 5000 permutation thresholding). Color bars indicate the numbers of lesion overlap or Z-scores. White numbers over slices indicate Montreal Neurological Institute (MNI) z-coordinates.

Table. 1 Baseline characteristics of subjects.

	CPD group (n=50)	Control group (n=69)	p value
Age (years)	68.6±11.6	63.5±10.7	**0.015***
Sex (M/F)	31/19	34/35	0.169
Etiology (Hemorrhage/Infarction)	18/32	33/36	0.198
Sides of lesioned hemisphere (Right/Left/Bilateral)	15/12/23	27/18/24	0.436
Duration from onset to VFSS (days)	64.8±41.4	56.9±45.4	0.327
Lesion volume (voxels)	15434.8±8551.7	14339.7±8495.963	0.490
FDS	44.5±13.9	12.1±6.7	**<0.001***

Continuous variables are expressed as mean ± standard deviation. * $p<0.05$

CPD: CricoPharyngeal Dysfunction, VFSS: Video Fluoroscopic Swallowing Study, FDS: Functional Dysphagia Scale

Table 2. Significant regions associated with A) prevalence of post-stroke CPD using Liebermeister statistics, and B) severity of post-stroke CPD after adjustment for age and total lesion volume using Freedman-Lane multivariable regression.

A)

Peak ROI	Peak Z MNI coordinate			Peak Intensity† (Z-scores)	Volume (voxels)	Composition
	x	y	z			
R Globus Pallidus	20	0	-6	5.42	73	56.2% R Globus Pallidus; 35.6% R Putamen
R Middle Frontal lobe	28	26	30	4.93	95	96.8% R Frontal lobe

B)

Peak ROI	Peak Z MNI coordinate			Peak Intensity‡ (Z-scores)	Volume (voxels)	Composition
	x	y	z			
R Rectus Gyrus	16	18	-12	5.53	27	100% R Frontal lobe
R globus pallidus	20	-2	-4	6.91	166	44.6% R Globus Pallidus; 33.7% R Putamen
L Orbital gyrus	-18	44	-10	5.2	15	100% L Frontal lobe
R Middle frontal lobe	28	26	30	6.01	808	97.3% R Frontal lobe
L Medial Frontal Gyrus	-20	46	-2	5.59	12	91.7% L Frontal lobe

Minimum 10 voxels in acquired space.

CPD: CricoPharyngeal Dysfunction, ROI: Region Of Interest, R: Right

† Liebermeister Z-scores

‡ Z-scores of Freedman-Lane multivariable regression