

Background

- Vascular Cognitive Impairment (VCI)** is defined as cognitive impairment attributable to vascular risk factors and vascular pathologies.¹
- Diagnosis of VCI:** (1) history of stroke or evidence of vascular disease on neuroimaging (2) neuropsychological testing should demonstrate cognitive deficits.²
- In 2006 the National Institute of Neurologic Disorders and Stroke and the Canadian Stroke Network (NINDS-CSN) developed the Vascular Cognitive Impairment Harmonization Standards (VCIHS), a neuropsychological assessment of cognition that evaluates language, memory, visuospatial, and executive functions¹
- English³, French⁴, Chinese⁵ and Korean⁶ adaptations of the VCIHS have been developed and their utilities have been assessed.
- However, validation of the VCIHS using extensive MRI guided brain volumetric analyses to assess the influences of vascular neuro-pathology on each facet of cognition have not been explored.

Purpose

We studied patients with acute ischemic stroke to:

- Achieve MRI guided validation of the Korean-VCIHS
- Determine neuropathologic substrates of VCI on MRI by investigating the associations between (i) brain atrophy, (ii) infarct volume, and (iii) degree of white matter hyperintensity (WMH) and the Korean-VCIHS.

Methods

1. Study Participants

- 50 participants with acute ischemic stroke were recruited
- Inclusion criteria:** no other neurodegenerative diseases, and able to complete the VCIHS

2. Magnetic Resonance Imaging

- T1-weighted, T2-weighted, Diffusion Weighted Imaging (DWI), and FLAIR images were acquired on 1.5T Philips MRI scanner at Hallym University Hospital in South Korea within four days of stroke event

3. Image Processing

- Acutely infarcted tissues (hyperintense on DWI) and previous covert infarctions (hypodensity on T1) were traced using ANALYZE 8.0 software.
- WMH on FLAIR images were assessed using a semi-automated fuzzy lesion extractor (FLEX) pipeline⁷
- T1-based brain tissue segmentation was achieved using a modified in-house Semi-Automatic Brain Region Extraction (SABRE) Pipeline⁸ See **Figure 1**.

4. Neuropsychological Assessment

- 3 months after stroke, MMSE (Mini-Mental State Exam) and the VCIHS were administered
- The VCIHS was comprised of 10 tests across 4 Cognitive Domains:

1. Memory Function

- Hopkins Verbal Learning Task (Immediate Recall, Delayed Recall and Recognition)

2. Executive Function

- Trails Making Test-Part A and Part-B
- Controlled Oral Word Association Test (Phonemic)

iii. Digit Symbol Coding

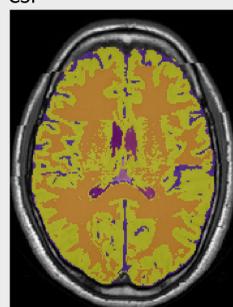
3. Visuospatial Function

- Ray Complex Figure Task Copy

4. Language Function

- Boston Naming Test
- Controlled Oral Word Association Test (Animal)

Figure 1: Segmentation results on T1 weighted MRI. Legend: (1) Purple; sulcal CSF (2) Yellow; normal appearing GM (3) Orange; normal appearing WM (4) Pink, Ventricular CSF



Methods

5. Statistical Analysis

- Using Microsoft SPSS 20.0 Software Multiple linear regression analyses with backwards elimination of non-significant variables were performed
- Brain Parenchymal Fraction (BPF), stroke volume, WMH volume, and the ARWMC scale as predictors of (i) Executive Function (ii) Memory (iii) Visuospatial Function and (iv) Language Function
- Age, sex, education and strategic stroke location were controlled for in all analyses

Results

Table 1: Demographic and Cognitive Data

Variable	Mean ± SD
Age (years)	64.22 ± 14.03
Education (years)	8.96 ± 5.13
Gender (Male:Female)	21:28
NIHSS	2.91 ± 2.71
MMSE	24.27 ± 5.07
KVCIHS Executive Domain z score	-1.44 ± 1.58
KVCIHS Memory Domain z score	-0.72 ± 0.94
KVCIHS Language Domain z score	-0.99 ± 1.00
KVCIHS Visuospatial Domain z score	-0.58 ± 2.63
KVCIHS Global Cognitive (avg10) z score	-1.08 ± 1.18
KVCIHS Global Cognitive (avg4) z score	-0.93 ± 1.32

Table 2: Volumetric Data*

Variable	Mean ± SD
White Matter Volume (mL)	437.51 ± 73.81
Gray Matter Volume (mL)	592.95 ± 94.58
Ventricular CSF Volume (mL)	30.55 ± 17.27
Sulcal CSF Volume (mL)	221.01 ± 47.637
WMH Volume (mL)	4.64 ± 5.74
Infarction Volume (mL)	7.10 ± 10.40
NABPF	0.797 ± 0.042

* Volumetric data shown here are raw values, but these were head size corrected for regression analyses

Table 3: Summary of Multiple Regression Analyses

	Variable	Standardized β	p-value	r ²
Executive Function	Model 1 (N=49)			
	Total Infarction Volume	-0.349	0.014	0.12
	Global WMH Volume	-0.381	0.01	0.14
Memory Function	Model 3 (N=49)			
	Total Infarction Volume	-0.377	0.007	0.14
Visuospatial Function	Model 4 (N=49)			
	NABPF	0.309	0.031	0.09
Language Function	Model 5 (N=35)			
	Total Infarction Volume	-0.423	0.009	0.17
K-VCIHS Global Cognitive Score (average of 10 tests)	Model 6 (N=49)			
	NABPF	0.254	0.071	0.06
K-VCIHS Global Cognitive Score (average of the 4 domain scores)	Model 7 (N=49)			
	Total Infarction Volume	-0.400	0.004	0.16
K-VCIHS Global Cognitive Score (average of 4 domains)	Model 8 (N=49)			
	NABPF	0.566	0.004	0.16

- Model 2:** Analysis of Supratentorial Infarction group
- Model 5:** Analysis of Right Hemisphere strokes
- Model 7:** VCIHS average Z score of 10 neuropsych tests
- Model 8:** VCIHS average z score of 4 neuropsych Domains

Figure 2: Partial Regression Plots (A) Total executive score as a function of WMH in supratentorial infarction (B) K-VCIHS Global Cognitive Score average of 4 cognitive domains

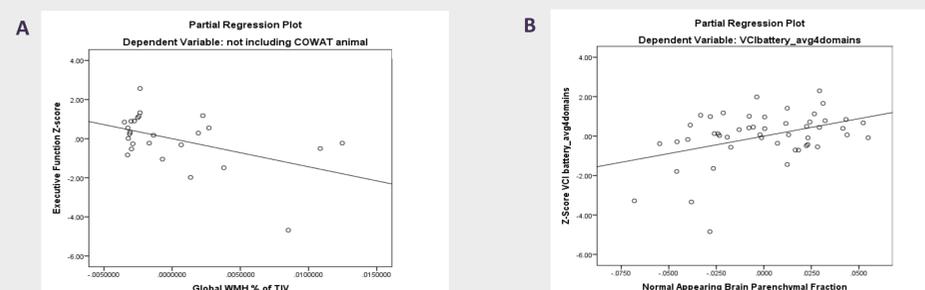
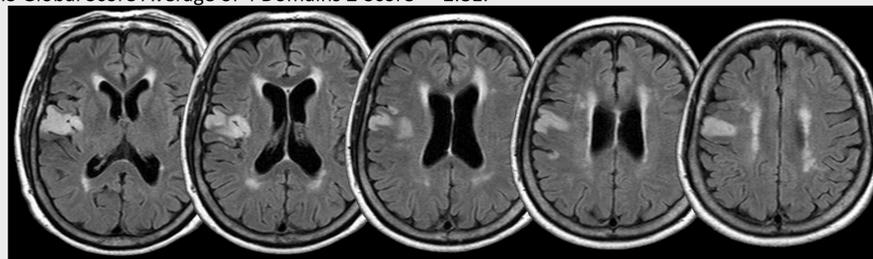
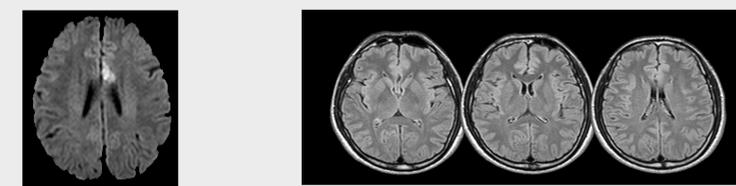


Figure 3: FLAIR image of a 73 year old patient with executive dysfunction (z = -3.71), Right Frontal-insular infarction (12.75 mL or 0.97% of TIV), substantial WMH (10.00mL or 0.76 % of TIV) and mild atrophy (NABPF=0.76). MMSE = 15 and 7 years of education. K- VCIHS Global Score Average of 10 tests Z-Score = -2.69. K- VCIHS Global Score Average of 4 Domains Z-Score = -2.81.



Results

Figure 4: DWI (left) and FLAIR (right) images of a 37 year old patient, with left medial-superior frontal lobe infarction (1.92 mL or 0.14% of TIV), no WMH (0mL), minimal atrophy (NABPF=0.87). MMSE = 28 and 16 years of education. K- VCIHS Global Score Average of 10 tests Z-Score = -1.02. K- VCIHS Global Score Average of 4 Domains Z-Score = -0.65. Executive Z-Score = -1.86.



Discussion and Conclusion

- Executive dysfunction was the most common feature in this cohort with VCI, suggesting that VCI oriented global cognitive measures should adequately assess executive function
- The **K-VCIHS Global Score (Average of 10 Tests)** allots 40% of its score to executive function, while each cognitive domain in the **K-VCIHS Global Score (Average of 4 Cognitive Domains)**, has a 25% contribution to the overall cognitive score
- Executive function in the whole sample of stroke patients (model 1), was related to ischemic infarction volume. However, in patients with supratentorial strokes (model 2; Figure 2A), executive function was also related to global WMH volume.
- This study also has implications for calculating global cognitive scores from individual test scores, as different brain behavior relationships were noted depending on how the Global VCIHS Z-score was calculated:
 - While the **K-VCIHS Global Score (Average of 4 Cognitive Domains)**, was associated with brain atrophy (model 8), the **K-VCIHS Global Score (Average of 10 Tests)** was associated with infarction volume (model 7).
- Overall, these results suggest that the Korean adaptation of the NINDS-CSN VCIHS-NP is reflective of the varying effects of brain atrophy, white matter hyper-intensities and stroke lesions on cognition
- We also identify plausible neuroimaging substrates of VCI:
 - Brain Atrophy:** Global cognition and visuospatial function
 - White Matter Hyperintensity:** Executive function in those with supratentorial stroke
 - Infarction Volume:** Global cognition, memory, executive function, visuospatial function

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