Cognitive Impairment Evaluated With Vascular Cognitive Impairment Harmonization Standards in a Multicenter Prospective Stroke Cohort in Korea

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Background and Purpose—Since the Vascular Cognitive Impairment Harmonization Standards (VCIHS) neuropsychological test protocol was proposed by the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network, no studies have applied this neuropsychological protocol to poststroke survivors in a large-scale, multicenter stroke cohort. We determined the frequency of vascular cognitive impairment (VCI) and investigated the feasibility of using the Korean version of the VCIHS neuropsychological protocol in a multicenter, hospital-based stroke cohort in Korea.

Methods—We prospectively enrolled 620 subjects with ischemic stroke within 7 days of symptom onset among 899 patients who were consecutively admitted to 12 university hospitals in Korea. Neuropsychological assessments using the 60-minute Korean VCIHS neuropsychological protocol were administered at 3 months after stroke.

Results—Of the 620 patients, 506 were followed up at 3 months after stroke. Of these, 353 (69.8%) were evaluated for cognitive function using the 60-minute Korean VCIHS neuropsychological protocol. The frequency of VCI at 3 months was 62.6%: VCI with no dementia in 49.9% and vascular dementia in 12.7%. Old age (P=0.014), poor functional outcomes at 3 months (P=0.029), and stroke subtypes other than small vessel disease (P=0.004) were independent risk factors of VCI.

Conclusions—VCI, evaluated using the Korean VCIHS neuropsychological protocol, is substantial at 3 months after ischemic stroke in Korea. The use of the 60-minute Korean VCIHS neuropsychological protocol was feasible in large-scale multicenter studies. (Stroke. 2013;44:786-788.)

Key Words: neuropsychology ■ stroke ■ vascular dementia

Several studies have elucidated the frequency and characteristics of cognitive dysfunction in stroke patient cohorts. However, most studies of poststroke cognitive impairment have focused on dementia. In 2006, the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network proposed the Vascular Cognitive Impairment Harmonization Standards (VCIHS), which could be used to evaluate cognitive dysfunction in potential patients with vascular cognitive impairment (VCI) in multicenter studies. However, no study has applied this neuropsychological test protocol to poststroke survivors in a large-scale, multicenter stroke cohort. The purpose of this study was to determine the frequency of VCI and to investigate the usefulness of the Korean version of the VCIHS neuropsychological (K-VCIHS-NP) protocol in a multicenter, hospital-based stroke cohort study in Korea.

Methods

From October 2007 to August 2008, we screened 899 ischemic stroke patients among who consecutively enrolled to the hospital-based stroke registers of 12 university hospitals in South Korea. The ischemic stroke was confirmed by magnetic resonance imaging within 7 days of symptom onset. Of these patients, a total of 620 were enrolled within 2 weeks after stroke for baseline evaluations. At 3 months after stroke, 506 patients underwent a follow-up evaluation, and 353 patients completed the 60-minute K-VCIHS-NP protocol proposed by the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network (Figure). Korean Mini-Mental Status Examination for evaluating global cognitive dysfunctions and the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) for the premorbid history of cognitive functions were also included. The tests and scales that compose the K-VCIHS-NP protocol were validated and standardized for Korean subjects (online-only Data Supplement Table I).

Dementia was diagnosed with reference to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, criteria based on cognitive functions that were categorized as impaired when a score was below the 10th percentile for an individual domain and social functioning status as assessed by the Instrumental Activities of Daily Living scale. Patients were classified as having vascular dementia (VaD), VCI with no dementia, and normal cognition. The detailed methodology is described in the online-only Data Supplement.
Results

Of 620 patients enrolled in baseline evaluation, 267 missed the cognitive assessment follow-up at 3 months, as depicted in the Figure. Patients who were lost to follow-up were older, less educated women, and had more hypertension, previous stroke, severe stroke symptoms when admitted, and worse prestroke functional and cognitive status (online-only Data Supplement Table II).

The number of subjects with VCI at 3 months after stroke was 221 (62.6%) of the 353 poststroke survivors who completed the K-VCIHS-NP protocol; VCI with no dementia was apparent in 176 (49.9%), and VaD was apparent in 45 (12.7%). As defined by the Korean Mini-Mental Status Examination scores, the frequencies of VCI with no dementia and VaD were 9.9% (35/353) and 16.4% (58/353), consecutively. The proportion of patients with recurrent stroke who experienced VaD was twice that of first-ever stroke patients (21.5% vs 10.8%; Table). The frequency of prestroke cognitive decline evaluated using Korean-IQCODE at the time of admission was 7.2% (25/346) among patients who completed the 3-month follow-up. The frequency of VaD among patients who had experienced prestroke cognitive decline was 40% (10 of 25), which was ≈4-times higher than the frequency among patients who did not have prestroke cognitive decline (10.3%; 33/321). Old age (P=0.014), poor functional outcomes at 3 months poststroke (P=0.029), and stroke subtypes other than small vessel disease (P=0.004) were independent risk factors of VCI (Online Table III).

Discussion

To the best of our knowledge, this is the first large-scale, multicenter study to evaluate the frequency of VCI using the 60-minute K-VCIHS-NP protocol proposed by the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network.

A substantial percentage of patients in the prospective acute stroke cohort were unable to undergo cognitive assessment because of death, worsening of neurological or medical conditions, or failure to follow-up. In this study, of the 506 patients who were followed-up at 3 months after stroke, 353 patients (69.8%) were evaluated using the K-VCIHS-NP protocol (Figure). This coverage rate of cognitive assessment was slightly lower than the rates from previous studies, which were reported to be 74.0% to 76.5%.3,4,8 However, the previous cohort studies were not conducted in a multicenter setting, and they applied individual neuropsychological tests, such as the IQCODE or the Mini-Mental Status Examination.2,5–7

Table. Frequency of Cognitive Impairment at 3 Months After Stroke in Different Study Populations

<table>
<thead>
<tr>
<th>Variable</th>
<th>VaD</th>
<th>VCIND</th>
<th>Normal Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects, n=353</td>
<td>12.7% (45)</td>
<td>49.9% (176)</td>
<td>37.4% (132)</td>
</tr>
<tr>
<td>First-ever stroke, n=288</td>
<td>10.8% (31)</td>
<td>51.4% (148)</td>
<td>37.8% (109)</td>
</tr>
<tr>
<td>Recurrent stroke, n=65</td>
<td>21.5% (14)</td>
<td>43.1% (28)</td>
<td>35.4% (23)</td>
</tr>
<tr>
<td>Prestroke cognition, n=346</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declined cognition, n=25 (K-IQCODE ≥3.6)</td>
<td>40.0% (10)</td>
<td>52.0% (13)</td>
<td>8.0% (2)</td>
</tr>
<tr>
<td>Normal cognition, n=321 (K-IQCODE &lt;3.6)</td>
<td>10.3% (33)</td>
<td>49.8% (160)</td>
<td>39.9% (130)</td>
</tr>
</tbody>
</table>

K-IQCODE indicates Korean-Informant Questionnaire of Cognitive Decline in the Elderly; VaD, vascular dementia; and VCIND, vascular cognitive impairment with no dementia.

Figure. Subject disposition.
experienced cognitive dysfunctions before stroke. Because pre-stroke cognitive decline had to be retrospectively evaluated using the K-IQCODE in this hospital-based study setting, the prevalence of pre-stroke dementia could be underestimated. However, the progression of patients from pre-stroke cognitive decline to VaD observed in this study was similar to that of a previous cohort study. In conclusion, the 60-minute K-VCIHS-NP protocol might be useful for evaluating cognitive impairments in poststroke survivors in multicenter cohort studies.

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Korean VCIHS study group members include Hee-Jun Bae, Jae-Kwan Cha, Ki-Hyun Cho, Soo-Jin Cho, San Jung, Yeonwook Kang, Dong-Eog Kim, Hahn-Young Kim, Oeun-Kyu Kim, Yong-Jae Kim, Im-Suck Koh, Sun-Uck Kwon, Ju-Hun Lee, Soo-Ju Lee, Mi Sun Oh, Jong-Moo Park, Joon-Hyun Shin, Kyung-Ho Yu and Byung-Chul Lee.

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Disclosures
None.

References
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SUPPLEMENTAL MATERIAL

Cognitive impairment evaluated with Vascular Cognitive Impairment Harmonization Standards in a multicenter prospective stroke cohort in Korea

Supplemental Methods

Participants

From October 2007 to August 2008, we screened 899 ischemic stroke patients with ischemic stroke among the consecutively enrolled to the multicenter hospital-based stroke register1 from 12 hospitals in South Korea. All subjects were patients with ischemic stroke diagnosed using diffusion-weighted MRI within 7 days of symptom onset.

Of these 899 patients, a total of 620 patients were enrolled for baseline assessment in this study, after excluding 79 patients with severe concomitant medical or neurological conditions (persistent impairment of consciousness or visual impairment), 14 with severe dysphasia, 8 who died within 2 weeks of stroke onset, 16 who were referred to other hospitals, and 162 who refused to give informed consent. The demographics, vascular risk factors, and clinical characteristics, including stroke subtypes, the severity of neurological symptoms, and functional status, were evaluated within 2 weeks after stroke onset during baseline evaluation. Of the 620 patients, 506 were followed up at 3 months after stroke onset, and 353 of them underwent comprehensive cognitive evaluations. This study was approved by the Institutional Review Board of each participating hospital, and all subjects provided written
informed consent.

Evaluation of cognitive functions

Three months after stroke, the patients’ cognitive functions were assessed using the 60-minute Korean version of the Vascular Cognitive Impairment Harmonization Standards neuropsychological (K-VCIHS-NP) protocol proposed by the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network. The original version consists of 4 cognitive domains: 1) executive / activation: Animal naming, Controlled Oral Word Association Test (phonemic fluency), Digit Symbol Coding, and Trail Making Test; 2) language: Boston Naming Test; 3) visuospatial: Rey Complex Figure Test: Copy--; and 4) memory: Hopkins Verbal Learning Test. In addition, Korean Mini-Mental Status Examination (K-MMSE) for evaluating global cognitive dysfunctions and the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) for assessing the patients’ pre-morbid history of cognitive dysfunctions were also included. All tests and scales in the original version were validated and standardized in Korea (Table S1).

Diagnosis of dementia and cognitive impairment

Dementia was diagnosed according to the Diagnostic and Statistical Manual (DSM) of Mental Disorders, Fourth Edition, criteria based on clinical interviews, cognitive functions assessed using the 60-minute K-VCIHS-NP, and social functioning status assessed on the scale of instrumental Activities of Daily Living (IADL) 3 months after stroke onset.
Cognitive functions were categorized as impaired when a decline was observed in at least 1 domain, where a score below the 10th percentile for an individual domain. For frontal domains, which consisted of 4 tests, patients who scored below the 10th percentile on more than 2 tests were identified as having abnormal frontal functions. Functional status and pre-stroke cognitive declines were classified as abnormal if the scores were above 0.43 on the Korean instrumental ADL scale\textsuperscript{5} and 3.6 on the K-IQCODE,\textsuperscript{12} in accordance with the validation studies conducted on the Korean versions of these tests.

Patients were classified as having vascular dementia (VaD), vascular cognitive impairment with no dementia (VCIND), and normal cognition. VaD was defined as dementia in post-stroke survivors without regard to pre-stroke cognitive status, and VCIND was defined as cognitive impairment after stroke that does not meet the dementia criteria of DSM-IV. We also compared the rates of VCIND and VaD defined by the K-VCIHS-NP protocol with the rates determined using more established neuropsychological instruments, K-MMSE scores. The subjects had a score below the 2nd percentile of the K-MMSE score of the norm group were defined as VaD, and between the 2nd and 10th percentile were VCIND.\textsuperscript{7,14-17}

Statistical Analysis

The differences in demographics and clinical variables between study participants and patients who were excluded from the study were compared using the Chi-squared and the Mann-Whitney tests according to the characteristics of variables. The clinical determinants associated with VaD, VCIND, and normal cognition were assessed using logistic regression models, controlling for age, sex, level of education, various
vascular risk factors, and other detailed clinical variables, including subtypes of ischemic stroke. A two-sided p-value of less than 0.05 was defined as statistically significant.
## Supplemental Table 1. Korean version of the 60-minute Vascular Cognitive Impairment Harmonization Standards-Neuropsychology Protocol proposed by the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network

<table>
<thead>
<tr>
<th>Cognitive domains and neuropsychological test</th>
<th>Korean version of VCIHS-NP protocol</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Executive/Activation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal naming (semantic fluency)</td>
<td>Animal naming</td>
<td>Kang, Y et al. (2000)⁸</td>
</tr>
<tr>
<td>Controlled Oral Word Association Test (COWAT)</td>
<td>Korean-COWAT (ㄱ ㅚ ㅅ)</td>
<td>Kang, Y et al. (2000)⁸</td>
</tr>
<tr>
<td>Digit Symbol Coding</td>
<td>Digit Symbol Coding</td>
<td>Yum, TH et al. (1992)⁶</td>
</tr>
<tr>
<td>Trail Making Test</td>
<td>Korean-Trail Making Test-Elderly’s version</td>
<td>Yi, H et al. (2007)¹⁸</td>
</tr>
<tr>
<td>List learning test strategies</td>
<td>Seoul Verbal Learning Test</td>
<td>Kang, Y et al. (2003)¹⁰</td>
</tr>
<tr>
<td><strong>Language / Lexical Retrieval</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>Korean-Boston Naming test: Short form A</td>
<td>Kang, Y et al. (1999)⁹</td>
</tr>
<tr>
<td><strong>Visuospatial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey Complex Figure Test: Copy</td>
<td>Rey Complex Figure Test: Copy</td>
<td>Kang, Yet al. (2003)¹⁰</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination (MMSE)</td>
<td>Korean-MMSE</td>
<td>Kang, Y (2006)⁷</td>
</tr>
<tr>
<td>Instrumental Activities of Daily Living (ADL)</td>
<td>Korean-Instrumental ADL</td>
<td>Kang, SJ et al. (2002)⁵</td>
</tr>
</tbody>
</table>

VCIHS-NP: Vascular Cognitive Impairment Harmonization Standards neuropsychological
Supplemental Table 2. Comparison of the clinical characteristics of patients whose cognitive function was evaluated with those of patients who dropped out at the 3-month follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline assessment (N=620)</th>
<th>Cognitive function evaluated (N=353)</th>
<th>Dropped out (N=267)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ± SD</td>
<td>65.6 ± 12.5</td>
<td>63.9 ± 12.4</td>
<td>67.9 ± 12.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (women), % (N)</td>
<td>44.4 (275)</td>
<td>38.8 (137)</td>
<td>51.7 (138)</td>
<td>0.002</td>
</tr>
<tr>
<td>Education, years ± SD</td>
<td>4.5 ± 1.8</td>
<td>4.7 ± 1.7</td>
<td>4.2 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk Factors, % (N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>66.3 (411)</td>
<td>62.9 (222)</td>
<td>70.8 (189)</td>
<td>0.046</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32.9 (204)</td>
<td>32.6 (115)</td>
<td>33.3 (89)</td>
<td>0.871</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>24.5 (151)</td>
<td>22.9 (80)</td>
<td>26.6 (71)</td>
<td>0.310</td>
</tr>
<tr>
<td>Smoking</td>
<td>43.2 (268)</td>
<td>45.9 (162)</td>
<td>39.7 (106)</td>
<td>0.130</td>
</tr>
<tr>
<td>prior stroke</td>
<td>23.2 (144)</td>
<td>18.7 (66)</td>
<td>29.2 (78)</td>
<td>0.002</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>17.6 (109)</td>
<td>15.9 (56)</td>
<td>19.9 (53)</td>
<td>0.206</td>
</tr>
<tr>
<td>NIH Stroke Scale score at admission (median*)</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Poor pre-morbid status, % (N)</td>
<td>9.8 (61)</td>
<td>7.6 (27)</td>
<td>12.7 (34)</td>
<td>0.048</td>
</tr>
<tr>
<td>(modified Rankin Score ≥3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-stroke IQCODE score, median*</td>
<td>3.07 (N=594)</td>
<td>3.07 (N=346)</td>
<td>3.11 (N=248)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

SD: standard deviation; N: number; NIH: National Institutes of Health; IQCODE: Informant Questionnaire of Cognitive Decline in the Elderly; * Mann-Whitney U test
<table>
<thead>
<tr>
<th></th>
<th>Normal cognition (N=132)</th>
<th>VCI (N=221)</th>
<th>P value</th>
<th>Adjusted OR(^\dagger)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men, %</strong></td>
<td>60.7</td>
<td>61.7</td>
<td>0.860</td>
<td>0.77 (0.42-1.41)</td>
<td>0.395</td>
</tr>
<tr>
<td><strong>Age, years (SD)</strong></td>
<td>59.9 (13.2)</td>
<td>66.5 (11.7)</td>
<td>&lt;0.001*</td>
<td>1.03 (1.01-1.06)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Low education, ≤ 6 years %</strong></td>
<td>35.1</td>
<td>46.0</td>
<td>0.055</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>49.1</td>
<td>69.2</td>
<td>&lt;0.001*</td>
<td>1.71 (0.94-3.12)</td>
<td>0.082</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>25</td>
<td>36</td>
<td>0.039*</td>
<td>1.47 (0.78-2.75)</td>
<td>0.234</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>27.7</td>
<td>20.6</td>
<td>0.142</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking, %</td>
<td>43.1</td>
<td>44.3</td>
<td>0.837</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior stroke, %</td>
<td>16.1</td>
<td>20.2</td>
<td>0.350</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ischemic Stroke subtypes, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>28.8</td>
<td>46.1</td>
<td>0.002*</td>
<td>1.42 (0.70-2.87)</td>
<td>0.331</td>
</tr>
<tr>
<td>Small vessel occlusion</td>
<td>40.5</td>
<td>21.3</td>
<td>&lt;0.001*</td>
<td>0.36 (0.18-0.72)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>12.6</td>
<td>17.6</td>
<td>0.239</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other or undetermined causes</td>
<td>8</td>
<td>14.7</td>
<td>0.425</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological severity on admission by NIH Stroke Scale, mean (SD)</td>
<td>3.45 (3.76)</td>
<td>4.57 (4.65)</td>
<td>0.025*</td>
<td>1.04 (0.97-1.13)</td>
<td>0.276</td>
</tr>
<tr>
<td>Poor functional status at 3 months by modified Rankin Scale ≥ 3, %</td>
<td>4.7</td>
<td>22.3</td>
<td>&lt;0.001*</td>
<td>3.59 (1.14-11.30)</td>
<td>0.029</td>
</tr>
</tbody>
</table>
NIH: National Institutes of Health; SD: Standard deviation; VCI: vascular cognitive impairment,
* Chi-square test, † Mann-Whitney test, ‡ OR: odds ratio (95% confidence interval) after adjusting for age, sex, hypertension, diabetes, NIH Stroke scale, modified Rankin Scale, large artery atherosclerosis, and small vessel occlusion

Supplemental References


version of Controlled Oral Word Association Test (COWAT) in the elderly


