Cognitive impairment after cerebrovascular stroke: Relationship to vascular risk factors


Background: Cognitive decline after cerebrovascular stroke has adverse outcome consequences. Since some vascular causes can be prevented and treated, the identification of stroke-related cognitive impairment is a challenge. Patients with cognitive impairment and vascular diseases exhibit higher homocysteine (Hcy) concentrations. Whether Hcy is an independent risk factor for cognitive impairment after stroke is still in question. The objectives of this study were to determine: 1) the relative frequency of first-ever post-stroke dementia (PSD) (three months after onset) in a consecutive sample of our population, 2) the risk factors associated with PSD, and 3) the relationship between Hcy levels and PSD.

Methods: Eighty-one inpatients with first-ever stroke were prospectively evaluated with a neuropsychological battery and event-related evoked potentials (P300) at onset and then after three months. A wide range of demographic, clinical, radiological and laboratory variables were examined. PSD was diagnosed if the clinical presentation fulfilled DSM-IV criteria of vascular dementia, the patient scored ≥21 on Mini Mental State Examination (MMSE) and ≥67 points on Cognitive Abilities Screening Instruments (CASI).

Results: PSD was diagnosed in 21%. PSD was significantly associated with increasing age, low levels of education, large sized and lacunar infarctions, severity of stroke, prolonged P300 latency, smoking, hypertension, and elevated Hcy levels. High Hcy levels increased the odds ratio of PSD after adjustment of significantly relevant variables including age, smoking, size of infarction, and carotid stenosis.

Conclusions: Cognitive decline is common after stroke. The results of this study indicate that PSD may result from stroke and its related risk factors including possible direct association with high Hcy levels. Better knowledge of the risk factors for PSD should increase the effectiveness of preventive strategies in patients with this condition.

Keywords: post-stroke dementia, vascular risk factors, homocysteine

Introduction

Cerebrovascular stroke (CVS) is the third leading cause of death and a major source of disability and mortality. CVS may result in quantifiable decrease in quality of life which is determined not only by the neurological deficits but also by impairment of cognitive functions. Post-stroke dementia (PSD) is a subtype of vascular dementia. Vascular dementia is the second most common type of dementia after Alzheimer’s disease (AD). PSD is defined as the presence of dementia identified at three months after an acute, either recurrent or first-ever, stroke. The frequency of PSD has been found to be higher than previously expected, and a stroke increases the risk of dementia 4 to 12 times. The prevalence of PSD among recurrent or first-ever stroke patients varies from 6% to 55%. Not all individuals with stroke develop dementia. In addition, the prevalence of PSD may decline years after stroke. Snaphaan and colleagues reported that the prevalence of post-stroke memory dysfunction varied from 23% to 55% three months after stroke, which declined from 11% to 31% one year after stroke. A further study of a stroke cohort indicated that >30% of subjects...
who had mild cognitive impairments between 0–6 months after stroke improved and were classified as cognitively intact by 12 to 18 months. These evidences indicate that PSD may be reversible in a substantial proportion of patients. In contrast, some studies found that not only the risk of PSD is high immediately after stroke but also remains higher in patients nondemented three months after stroke. Even among patients who remain cognitively intact, hospital-based and population-based studies have revealed a significant risk for developing delayed dementia. In community-based studies, the prevalence of PSD is about 30% and the incidence of new onset dementia after stroke increases from 7% after one year to 48% after 25 years.

The pathophysiology of PSD is multifactorial and its risk factors are still incompletely understood. In the past decade, raised plasma homocysteine (Hcy) has emerged as a potential risk factor for development of vascular diseases including coronary heart diseases and stroke. In addition, information has been emerging regarding a connection between Hcy metabolism and cognitive function, from mild cognitive decline to vascular dementia and AD. Only very few data are available regarding the direct impact of Hcy on cognitive in stroke patients. The direct relationship between variables related to post-stroke cognitive impairment and Hcy levels has to be studied. Also the results examining the relationship between Hcy and different stroke subtypes are inconsistent, controversial and there is no consensus about them. Since the possibility that Hcy is a risk factor for cognitive impairment after stroke and can be prevented and treated by vitamin supplementation, the identification of Hcy-related cognitive impairment after stroke is essential.

Aim of the work
This hospital-based study was done to determine 1) the relative frequency of first-ever PSD (three months after onset) in a sample of consecutive stroke patients of our population, 2) the risk factors of PSD, including demographic and clinical determinants, stroke characteristics including size, location, type, etiology, severity, and vascular risk factors, and 3) the relationship between total Hcy (tHcy) levels and cognitive decline after stroke.

Materials and methods
Included in this study were consecutive in-patients with recent CVS, aged 40–75 years, within seven days of stroke onset. Stroke was defined as acute onset of focal neurological deficits attributable to cerebrovascular disease and documented by computerized tomography (CT) or magnetic resonance imaging (MRI). Control healthy subjects (n = 40) were matched for age, sex, educational level, and socioeconomic status. Patients were recruited from the acute stroke unit of the Department of Neurology, Assiut University Hospital, Assiut, Egypt over a period of one year. Written consents were obtained from patients or their relatives after having received oral or written information about the study. The local ethical committee of Assiut University Hospital approved the study. Inclusion criteria for the study were: 1) Egyptian ethnicity; 2) well documented clinical presentation and CT and/or MRI scan of the brain after first acute stroke occurring within seven days before admission. Ischemic or hemorrhagic acute strokes and history of transient ischemic attacks were included; 3) ability to give consent or the availability of relative to give proxy consent to participate in the study; and 4) ability to have informed knowledge of the patients’ earlier and current cognitive functioning. Exclusion criteria included: 1) persistent disturbed level of consciousness; 2) persistent aphasia; 3) history of pre-stroke cognitive impairment; 4) missing baseline Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), which makes use of the informant’s knowledge of both the person’s earlier and current cognitive functioning; 5) history of psychosis or other neurological diseases involving the central nervous system that interfere with cooperation of patient; 6) brain ischemia due to cardiorespiratory arrest; 7) subarachnoid hemorrhage; 8) systemic diseases known to involve the central nervous system (as renal and liver diseases, systemic lupus erythematosus, and AIDS); 9) severe sensory impairment (blindness and deafness); 10) cancer discovered in the previous five years; and 11) patients with history of severe head trauma or neurosurgical operation at any time before stroke.

A standard stroke evaluation was conducted on admission in 370 consecutive patients admitted to stroke unit: 270 of those did not meet the selection criteria; 100 met the selection criteria; 12 refused to participate in the study; three died before the second assessment; and four had impaired cognitive function prior to stroke (pre-stroke dementia) as documented by IQCODE.

During the first week of stay in the stroke unit, patients’ relatives gave an account on the patients’ cognitive function by completing the IQCODE. It is a 26-item questionnaire that rates changes in everyday situations where a person has to use his memory or intelligence. Each situation is rated by the informant for amount of change over the previous 10 years, using a 5-point scale (1 = much better, 5 = much worse). The IQCODE is generally scored by averaging the ratings across
the 26 situations. A person who has no cognitive decline will have an average score of 3, while scores of >3 indicate cognitive decline. IQCODE has good crosscultural applicability and is used as a screening tool for dementia in a population with large variation in educational backgrounds.

Assessment procedures

Demographic and clinical characteristics
Baseline medical, neurological and psychiatric assessments were done within one week of admission. Demographic data included: age, sex, educational level, occupation, family history of dementia, family interview of pre-morbid status and history of stroke vascular risk factors (as smoking habits, hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation [AF], ischemic heart disease [IHD], and transient ischemic attacks). The educational level of the patients was measured as the total numbers of years of formal education each patient received (illiterate and educated for ≤8 years or >8 years). All patients were subjected to cardiac examination including an electrocardiogram (ECG) and echocardiography of the heart.

Laboratory measurements
Laboratory measurements included: serum tHcy, blood sugar (fasting and post-prandial), renal and liver functions and lipogram (serum total cholesterol [TC], triglycerides [TG], low-density lipoprotein cholesterol [LDL-c], high-density lipoprotein cholesterol [HDL-c]). Serum levels of TC, TG, HDL-c, and LDL-c were measured by an enzymatic colorimetric method using the autoanalyzer Hitachi 911 (Boehringer Mannheim, Indianapolis, IN, USA). tHcy was analyzed in blood using ELISA technique (Axis® homocysteine ElA package insert kits, IBL GmbH-Flughafenstrasse 52A-D-22335, Hamburg, Germany). The cut-off value of tHcy was 12 μmol/L.

Neuroimaging characteristics
A noncontrast CT brain scan examination was done for all patients while a MRI brain scan was done in selected patients (when CT revealed no abnormalities). The following radiological data were collected: presence of hemorrhage, infarct subtypes, number, size, location (deep versus superficial location), laterality of lesions and cerebral circulation involvement (territorial or lacunar). The stroke size was defined as: a) large if the infarction involved more than half a cerebral hemisphere; b) small if the infarction involved was >15 mm in diameter, but less than one half of a cerebral hemisphere; and c) lacunar if the infarction was <15 mm in diameter. Lacunar infarcts are localized to the territories of deep perforating arteries. Lesions were classified as superficial when they affected the cortical surface and/or subcortical white matter whereas deep lesions involved the basal ganglia, internal capsule, or thalamus. Patients with anterior circulation infarcts were associated with carotid arterial territory (left or right, anterior or middle cerebral arteries). Those associated with vertebrobasilar arterial territory were grouped under posterior circulation infarcts. The presumed causes of ischemic stroke were defined at discharge, according to the TOAST criteria (The Trial of Org 10172 in Acute Stroke Treatment) which categorizes ischemic stroke into five subtypes based on cause: large-artery atherosclerosis, small-artery occlusion (lacunes), cardioembolic stroke, stroke of other determined cause, and stroke of undetermined cause.20 The TOAST classification system for stroke has gained wide acceptance for both clinical and research purposes eg, stroke risk assessment studies as this study.

Carotid color duplex examination
Examination of the intima-media thickness of the carotid arteries (CA-IMT) was manually performed twice to all participants by the same experienced radiologist using a 5MHZ linear transducer of a color duplex flow imaging system (Acuson 128 XP, Acuson Corporation, Mountain View, CA, USA), which operates in several modes: real time B, color Doppler and spectral Doppler modes. We investigated the degree of stenosis in the common carotid artery (CCA). Significant stenosis of the cervical arteries, defined as a narrowing of ≥30% of the lumen.

Cognitive assessment
A detailed neuropsychological assessment was done twice for all patients, within one week of stroke onset and after three months. Normative data for these tests were also established twice in the control group.

A set of standardized neuropsychological tests which are sensitive for mild cognitive impairment and covering different cognitive domains, were selected. Each patient was tested on three separate days and at separate occasions in the same day to complete the total battery of testing and avoid exhaustion of stroke patients. The primary outcome variables for cognition were scored by the use of the following instruments: 1) Mini-Mental State Examination (MMSE),22 a widely used scale for the screening test for dementia. It consists of a variety of questions grouped into seven categories, each representing a different cognitive domain or function (orientation to time, orientation to place, repetition of words, attention, calculation,
recall of words, language, and visual construction). It has a maximum score of 30 points. As most of the subjects of the present study were illiterate or with low education levels, the two points testing reading and writing were excluded, and the full score was calculated as 28 instead of 30 points. The lower value for regarding a subject as dementia suspect was ≤21 instead of ≤23 points. MMSE takes 5–10 minutes to administer. 2) Cognitive Abilities Screening Instruments (CASI)23 is a 25-item test which provides quantitative assessment on attention, concentration, orientation, memories for past knowledge and present input, language or verbal fluency, drawing, constructional praxis, writing abilities, list generating abilities, abstract thinking, judgment, and everyday problem solving skills. The CASI is more comprehensive than most screening tests of cognitive abilities. The cut off of dementia was ≤67. It takes 45–60 minutes to administer. 3) Wechsler Memory Scale-Revised (WMS-R)24 is useful for mild memory impairment, where sensitivity is needed. Selected tests included: digit forward, digit backward, mental control, associate learning, logical memory I and II and visual reproduction I and II. It takes 25–30 minutes to administer.

Neurophysiological assessment
Testing for event-related potentials (ERPs) was done on a separate day after completion of neuropsychological battery of testing. It takes at least one and half hours to administer (as repetition of testing was needed to assure accuracy). Testing for ERPs was done twice for patients and controls (within one week and three months after stroke onset). ERPs are series of scalp waves that are extracted from the electroencephalogram (EEG) by time domain analysis and averaging of EEG activity following multiple stimulus repetitions. They were elicited with an auditory discrimination task paradigm by presenting a series of binaural 1.000 Hz (standard) versus 2,000 Hz (target) tones at 70 dB with a 10 millisecond rise/fall and 40 millisecond plateau time. Tones were presented at a rate of 1.1 per second, with target tones occurring randomly with a 0.2 probability. Subjects were sitting with their eyes closed and were instructed to mentally count the number of the target but not the frequent tones, and then asked to report the number of target tones counted at the end of each run. Potentials were recorded from scalp electrodes placed at Cz and were referred to linked ears. Filter settings were 0.5 and 70 Hz. Responses to 30 target and 120 nontarget tones were obtained in each trial. Separate averages for target and nontarget tones were obtained. Before recording, subjects were familiarized with the two tones and instructed to press a button when they heard target tones. The obtained ERPs were subdivided into early or sensory-evoked components (eg, P100, N100, P200, N200), which emerge within the first 100–200 millisecond after stimulus onset and basically reflect stimulus detection and auditory evoked brainstem potentials, and later or cognitive-related components (eg, P300).25 Latencies of each event-related component (N100, P200, N200, and P300) were measured. P300 latency was measured as the major positive peak after N200, within a range of 250–500 milliseconds. The amplitudes of N200 and P300 were measured peak to peak from the negative component just before the wave to the maximum positive peak of the wave. P300 is believed to index stimulus significance and the amount of attention allocated to the eliciting stimulus event, being maximal to task-relevant or attended stimuli and being absent or small to task-irrelevant or unattended stimuli.25

Assessment of motor and functional disabilities
The degrees of patients’ motor and functional disabilities were determined using Scandinavian Stroke Scale (SSS)26 and Barthel Index (BI).27 Each takes <10 minutes to administer. Assessment of depression was done using Hamilton Depression Rating Scale.28 It is a 21-item version test measuring the severity of depressive symptoms. The cut off point of depression in this scale is >17. It takes ~15 minutes to administer.

Follow up assessment after three months
Patients were regularly followed up monthly through the out-patient neurology clinic of the University Hospital to control for the therapeutic measures and those for secondary prevention of CVS. Both patients and control subjects were similarly assessed twice, three months apart, using the same battery of neuropsychological and neurophysiological assessment. Vascular dementia was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).29 DSM-IV defines the predominant disturbance as a clinically deficient in cognition or memory that represents a significant change from previous level of function. PSD was diagnosed if the clinical presentation fulfilled DSM-IV criteria of vascular dementia as well as when the subject scored ≤21 on MMSE and ≤67 points on CASI. WMS-R was used to assess selected aspects for memory other than that in MMSE and CASI.

Statistical analysis
Data were expressed as means ± SD unless otherwise stated. Calculations were done with the statistical package SPSS for Windows (version 10.0; SPSS Inc., Chicago, IL, USA).
Patients were divided into two groups according to the diagnosis of dementia. Descriptive statistics was used to compare baseline characteristics using two-tailed Student t test for quantitative variables for contrast of means and χ² test for comparison of proportions. Nonparametric methods were used to evaluate the number of the parameters that were not normally distributed. Mann–Whitney U-test (MW) was used to compare unpaired data that had skewed distribution (as TC, LDL-c, HDL-c, TG, tHcy, and P300 amplitude) while the Wilcoxon signed-rank test was utilized to compare paired data (for cognitive performance results of neuropsychological testings). Logistic regression analyses were used to assess the relation between Hcy and other relevant risk factors. A univariate logistic regression was first performed using Hcy as a dependant variable and demographic, clinical and vascular risk determinants of PSD as independent variables. Variables that showed significant association with increased Hcy levels in the univariate analysis (ie, p < 0.05) were used in multiple logistic regression analysis to determine the independent relation between Hcy and that variables. Results were given as odds ratio (OR) for risk factors, with 95% confidence interval (CI). For all tests, values of P < 0.05 were considered statistically significant.

Results

The final sample was 81 patients, 54 males and 27 females, with mean age 57.7 ± 5.19 years (range: 40–75 years). Seventy-six (93.8%) patients had educational level below eight years. Sixty-eight (84%) patients had ischemic stroke and 13 (16%) had hemorrhagic stroke. Twenty patients (24.7%) had stroke of dominant hemisphere and 61 (75.3%) had stroke of the nondominant hemisphere. The mean score of Scandinavian Stroke Scale (SSS) was 41.4 ± 11.8 and 59.3 ± 26.3 for BI at the acute phase of stroke. Seventeen patients (21%) fulfilled the criteria of PSD at three months after stroke. The frequency of dementia in ischemic and hemorrhagic strokes were 76.5% (or 13/17) and 23.5% (or 4/17) of patients, respectively. The vascular lesions contributing to PSD were territorial infarcts or gross hemorrhages in 15 cases (88.2%) and small vessel lacunar lesions in six (35.3%). Depression was present in 29.4% and 23.4% of patients with and without PSD. At follow up, stroke patients with depression had significantly greater impairment of motor and functional abilities than nondepressed stroke patients.

Table 1 showed the distribution of demographic and clinical characteristics according to presence or absence of dementia. Compared with nondemented patients, patients with PSD were significantly older (p = 0.053), had low levels of education (p = 0.003) and disturbed level of consciousness at the onset (p = 0.045). While no significant association was identified between PSD and sex, However, when patients classified according to age groups (40–54, 55–64, and 65–75 years), there was a significant association between age and dementia in females (p = 0.003) and not in males. The majority of vascular risk factors were more frequent among patients with PSD, such as current smoking (p = 0.054), hypertension (p = 0.007), AF (p < 0.0001), IHD (p < 0.0001), family history of dementia (p < 0.0001), elevated Hcy levels (p < 0.0001), and carotid stenosis (p = 0.024). At onset SSS (p = 0.019) and BI scores (p = 0.026) were worse in PSD.

Table 2 showed the distribution relationship between the findings of neuroimaging and stroke-related variables according to presence and absence of dementia. Large size infarctions (P = 0.001), territorial infarctions in the distribution of left or right carotid arteries (P = 0.05) and dominant hemispheric lesions (P = 0.01) were more frequent in PSD. Patients with PSD had significantly more large artery atherosclerosis (P = 0.01), cardioembolic (P = 0.001) and hemorrhagic (P = 0.01) strokes than did nondemented patients.

Table 3 showed the results of neuropsychological testing. At three months after stroke onset, patients demonstrated significant reduction in the total score for MMSE (p < 0.01) and CASI (p < 0.05). Significant reductions were demonstrated with logical memory (p < 0.05), attention (p < 0.05), orientation (p < 0.01), associate learning (p < 0.001), drawing (p < 0.05), abstract thinking (p < 0.05), and visual reproduction (p < 0.05).

Table 4 showed the resulting ERPs (latencies and amplitudes). At three months after the onset of stroke, patients demonstrated significant prolongation in the latencies of N100, N200, P200, and P300 (p < 0.001). No gender difference in ERPs was identified.

Cognitive impairment as determined by CASI scoring was associated with age (r = −0.255, p < 0.05), level of education (r = 0.657, p < 0.001), large-sized infarctions (r = −0.655, p < 0.001), lacunar infarctions (r = −0.685, p < 0.001), BI (r = −0.465, p < 0.05), P300 latency (r = −0.540, p < 0.001), current smoking (r = −0.465, p < 0.01), hypertension (r = −0.365, p < 0.05), and tHcy levels (r = −0.743, p = 0.0001).

As shown in Table 5, tHcy levels were stratified into low (≤12 μmol/L) and high (>12 μmol/L) groups. Older ages (p = 0.005), sizable infarctions (p < 0.0001), carotid stenosis (p < 0.0001), smoking (p = 0.05), presence PSD (p < 0.0001) and delayed P300 latency (p < 0.0001) were significantly associated with elevated tHcy levels.
In multiple logistic regression analysis, after adjustment of age, the odds ratio (95% CI) of PSD was 4.5 (1.5–13.5) in the group with high Hcy compared with 2.7 (1.2–8.0) for the low risk group (p = 0.01). Furthermore, after adjustment of smoking, the odds ratio of cognitive impairment (95% CI) was 4.7 (1.7–14.2) in the group with high Hcy and 2.5 (1.5–7.3) in the low risk group (p = 0.02). After adjustment for size of the infarction, the odds ratio of PSD (95% CI) was 4.8 (1.8–14.7) in the group with high Hcy and 2.5 (1.2–6.5) in the low risk group (p = 0.01). After adjustment for carotid stenosis, the odds ratio of PSD (95% CI) was 5.9 (2.8–18.5) in the group with high Hcy and 3.5 (1.5–9.5) in the low risk group (p = 0.005).

Discussion
Cerebrovascular stroke (CVS) is a risk factor for impaired cognitive functioning. Not only physical handicapping but also cognitive dysfunction after CVS can adversely influence

### Table 1 Demographic, clinical, vascular risk factors and functional status of demented and nondemented patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Demented (n = 17)</th>
<th>Nondemented (n = 64)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>40–75</td>
<td>40–75</td>
<td></td>
</tr>
<tr>
<td>mean + SD</td>
<td>65.5 ± 9.2</td>
<td>56.9 ± 5.3</td>
<td>0.053</td>
</tr>
<tr>
<td><strong>Males/females (n = 27/54)</strong></td>
<td>11/6</td>
<td>43/21</td>
<td>0.847</td>
</tr>
<tr>
<td><strong>Level of education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>illiterate</td>
<td>14 (82.4%)</td>
<td>42 (67.7%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Less than eight years of education</td>
<td>3 (17.6%)</td>
<td>17 (36.6%)</td>
<td></td>
</tr>
<tr>
<td>More than eight years of education</td>
<td>0</td>
<td>5 (7.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Disturbed consciousness at onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>13 (76.5%)</td>
<td>24 (37.5%)</td>
<td>0.054</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (58.8%)</td>
<td>23 (35.9%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (58.8%)</td>
<td>31 (48.4%)</td>
<td>0.334</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>2 (11.8%)</td>
<td>21 (32.8%)</td>
<td>0.087</td>
</tr>
<tr>
<td><strong>Cardiac disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (29.4%)</td>
<td>1 (1.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6 (35.3%)</td>
<td>11 (17.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of dementia</td>
<td>6 (35.3%)</td>
<td>1 (1.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>2 (11.8%)</td>
<td>6 (9.4%)</td>
<td>0.769</td>
</tr>
<tr>
<td>Scandinavian Stroke Scale</td>
<td>35.4 ± 13.9</td>
<td>42.9 ± 10.8</td>
<td>0.019</td>
</tr>
<tr>
<td>Barthel Index scale</td>
<td>46.7 ± 2.8</td>
<td>62.7 ± 24.9</td>
<td>0.026</td>
</tr>
<tr>
<td>Presence of depression</td>
<td>5 (29.4%)</td>
<td>15 (23.4%)</td>
<td>0.412</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>52.3 ± 18.0</td>
<td>55.7 ± 14.5</td>
<td>0.620</td>
</tr>
<tr>
<td>Packed cell volume, %</td>
<td>36.3 ± 4.8</td>
<td>37.8 ± 3.5</td>
<td>0.750</td>
</tr>
<tr>
<td><strong>Homocysteine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>8 (47.05%)</td>
<td>14 (22%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Hcy level, μmol/L</td>
<td>17.9 ± 8.0</td>
<td>12.3 ± 3.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Lipid profile</strong></td>
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</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>81.9 ± 52.2</td>
<td>183.9 ± 45.1</td>
<td>0.870</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>112.5 ± 48.9</td>
<td>121.3 ± 53.7</td>
<td>0.545</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>104.35 ± 46</td>
<td>98.3 ± 45.4</td>
<td>0.620</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>54.2 ± 27.8</td>
<td>64.7 ± 34.1</td>
<td>0.242</td>
</tr>
<tr>
<td>Carotid stenosis (≥30%)</td>
<td>8 (47.1%)</td>
<td>13 (20.3%)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

**Notes:** Data are expressed as mean ± SD and number (%); significance is between demented and nondemented groups; ‘significance between illiterate/less than eight years of education and more than eight years of education; significance is set at p-value < 0.05.

**Abbreviations:** Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.
Risk factors for post-stroke dementia

the long-term survival after adjusting other predictors for stroke mortality.\textsuperscript{1,2} The frequency of dementia after CVS varies between studies. The results of this study revealed that dementia affects up to 21\% of stroke survivors three months after stroke. Jonkman and colleagues\textsuperscript{30} reported that the incidence of cognitive impairment three months after stroke was 35\%–37\%. Pohjasvaara and colleagues\textsuperscript{31} reported PSD in 31.8\%. Madureira and colleagues\textsuperscript{32} found the frequency of PSD to be only 6\%. Our finding falls between these extremes and is comparable to most of the literatures. The difference of prevalence of PSD among various studies depends on the study design (eg, nonprospective or nonconsecutive samples) and the population studied, eg. demographic characteristics (as age, gender, and ethnicity), criteria used for the diagnosis of dementia, clinical manifestations, the preexisting cognitive level, lesion-related and radiological-associated factors as exclusion of hemorrhage or recurrent stroke, white matter changes, presence of cerebral atrophy, vascular risk factors, the time interval between the stroke and the neuropsychological assessment and length of follow-up.\textsuperscript{1,4,7,8,12,30–33} In an exploratory effort, Tatemichi and colleagues\textsuperscript{7} reported PSD in 16\% (116/726) of patients in a stroke cohort aged ≥60 years. In a subsequent hospitalized cohort studied three months after stroke, PSD was found in 26\% (66/251).\textsuperscript{33} The identified lower frequency of PSD in this study may be related to exclusion of patients with persistent aphasia, patients with persistent disturbed consciousness, recurrent stroke, age >75 years, and the uses of DSM–VI as well as CASI and MMSE in the diagnosis of PSD.

In the present study, attention, orientation, calculation, language, and motor skills, logical memory, associate learning, visual reproduction, drawing, and abstract thinking were significantly involved in PSD. It has been suggested that there is no consistent phenotype for stroke-related
cognitive dysfunction because strokes can strike any region of the brain. If selected impaired cognitive functions are considered, 50%–75% of stroke patients are found to be affected, depending on age. The significant prolongation of P300 latencies of ERPs at three months after stroke onset, further supports the involvement of selected cognitive domains in PSD. The intracerebral origin of the P300 is poorly understood but most likely reflects the summation of multiple, simultaneously occurring cognitive and brain processes that are engaged during the active processing of behaviorally significant stimulus events and functionally linked to 1 resource allocation and memory updating operations in the brain. The hippocampus, thalamus, and frontal cortex are considered as possible locations of the P300 generators, these structures are important for learning and memory. P300 latency has been found to increase as the dementia symptoms increase. P300 latency is considered a consequence of attention process, speed of reaction, and immediate memory. The shorter P300 latencies indicate superior mental performance relative to longer latencies.

In the present study, demographic determinants for PSD included increasing age, low level of education, and family history of dementia. The risk of PSD increased with aging. Increasing age is an important risk factor for vascular diseases including CVS and vascular dementia. It has been recently suggested that an age-related decrease in the buffering capacities of both the vessels and the craniospinal cavity favors cerebral hypoxia and reduction in cerebral arterial inflow. The decreased total cerebral blood flow and the reduced proportional aqueductal and cervical cerebrospinal fluid pulsations are the result of arterial loss of pulsatility. The decreased cerebral blood flow with age is a factor for brain damage and cognitive decline. The increased risk of dementia in older females is consistent with some studies. Menopause is known to be associated with cognitive impair- ment. The estrogen depletion with age increases the incidence of vascular dementia.

Patients with low levels of education were more vulnerable to PSD than educated patients. Recent reports confirmed a real association between educational attainment and the risk of dementia 50 to 60 years later. It seems that
Table 4 Event-related potential components in patients (at onset and after three months) and control groups

<table>
<thead>
<tr>
<th>Item</th>
<th>Patients (Baseline)</th>
<th>Patients (After 3 months)</th>
<th>Controls (Baseline)</th>
<th>Controls (After 3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N100 latency (msec)</td>
<td>114.45 ± 37.65</td>
<td>146.84 ± 38.79</td>
<td>108.84 ± 12.43</td>
<td>111.34 ± 21.21</td>
</tr>
<tr>
<td>N200 latency (msec)</td>
<td>235.65 ± 38.12</td>
<td>260.65 ± 39.67</td>
<td>226.80 ± 13.59</td>
<td>228.99 ± 34.21</td>
</tr>
<tr>
<td>P100 latency (msec)</td>
<td>194.02 ± 41.59</td>
<td>213.41 ± 36.41</td>
<td>183.60 ± 16.19</td>
<td>189.99 ± 20.26</td>
</tr>
<tr>
<td>P100 amplitude (mv)</td>
<td>9.26 ± 3.72</td>
<td>8.18 ± 3.36</td>
<td>9.59 ± 8.57</td>
<td>10.32 ± 11.34</td>
</tr>
<tr>
<td>P200 latency (msec)</td>
<td>311.17 ± 41.85</td>
<td>330.04 ± 44.26</td>
<td>314.80 ± 10.50</td>
<td>310.76 ± 9.76</td>
</tr>
<tr>
<td>P200 amplitude (mv)</td>
<td>14.36 ± 5.69</td>
<td>17.83 ± 8.43</td>
<td>14.99 ± 8.61</td>
<td>16.89 ± 9.76</td>
</tr>
</tbody>
</table>

Notes: Data are expressed as mean ± SD. *p < 0.05, **p < 0.01: Baseline assessment patients versus controls; *p < 0.05, **p < 0.01, ***p < 0.001: Before treatment assessment versus after treatment.

Patients with higher educational attainment have larger functional cognitive reserve and also differences in lifestyle and risk factor profile which are protective against cognitive decline. Low levels of education were found to be associated with significant decline in incidental memory, psychomotor performance and perception. Animal studies confirmed that complex environmental stimuli promote dendritic growth and brain weight.

The relation between genetic factor and development of dementia in elderly has been previously reported. In accordance with this study, higher percentage of PSD was identified among patients with family history of dementia (35.3%) than in the nondemented group (1.6%).

In the present study, large infarcts, lacunar infarcts, dominant hemispheric lesions and motor and functional disability were more frequent among patients with PSD. Significant inverse association was identified between PSD and small and lacunar infarcts and severity of stroke.

The size, laterality, location of lesion(s) with particular reference to the extent of white matter damage, vascular territory involvement, hemispheric and cortical involvement are known as important determinants of cognitive dysfunction. The classic concept implies that dementia of vascular origin is the result of a critical volume of infarcted brain tissue, irrespective of its topography. PSD is well documented in patients with extensive subcortical white matter lesions. Large sized infarctions are expected to produce more cognitive impairment compared to small sized infarction unless the small infarcts are in strategic locations (eg, thalamus, corpus callosum, hippocampus) even when they are lacunar as identified also in this study. Vinters and colleagues recently described three pathogenic concepts of vascular dementias based on pathological and functional imaging data as follow: accumulated cortical infarcts; strategic subcortical infarcts and functional cortical disconnection.

Hemispheric dominance involvement was more frequent in patients with PSD. Several studies suggest that intelligence or cognitive efficiency relies heavily on the integrity of language processing and hemispheric dominance. Certain cortical lesions due to CVS may generate defined cognitive signs and symptoms (amnesia, aphasia, apraxia, alexia, agraphia). In combination with noncognitive abnormalities, such as emotional instability or loss of initiative, these lesions in various combinations and extensions may constitute a cortical dementia syndrome. Ballard and colleagues reported that the severity of expressive language performance at three months was associated with dementia at follow-up. In general, the degree of PSD commonly parallel that of motor and functional disability, however, some studies demonstrated that the degree of dementia did not always parallel that of neurological deficits.

Although many studies have been conducted for identification of vascular risk factors for PSD, however, their findings were inconsistent and controversial. In this study, current smoking, hypertension, AF, IHD, carotid stenosis and elevated Hcy levels were more frequent in patients with PSD. Significant inverse association was identified between PSD, smoking, and hypertension.

Current smoking was significantly associated with PSD. Recent studies revealed that smoking was associated with greater risk of poor memory in middle-aged and elderly individuals and ex-smokers had a lower risk of poor cognition. In multicenter cohort studies, higher rates of decline by smoking were found in men and women, persons with and without family history of dementia, and in three of four participating studies. Higher cigarette pack-year exposure was correlated with a significantly higher rate of decline. Ikeda and colleagues in their prospective case-control study conducted to examine the association between cigarette smoking and risk of disabling dementia within the cohort of 6,343 men and women aged 35–85 years, found that...
long-term cigarette smoking was associated with a great risk of disabling dementia. Furthermore, and contrary to early case-control studies which suggested that smoking protects against AD, recent prospective studies have shown that elderly who smoke may be at increased risk for dementia. In the recent observational study done by Almeida and colleagues, smoking was found to be associated with reduced cortical regional gray matter density in brain regions associated with AD. Anstey and colleagues assessed the association of smoking with dementia and cognitive decline in a meta-analysis of 19 prospective studies with at least 12 months of follow-up. Studies included a total of 26,374 participants (mean age: 74 years) followed up for dementia for 2–30 years and 17,023 participants followed up for 2–7 years. Over the follow-up period, current smokers at baseline were found to have a high risk for incident AD, vascular dementia, and greater yearly declines in MMSE compared with those who never smoked. Recent studies showed that smoking is significantly associated with low cerebral blood flow which compromises cognition.

Hypertension was significant following PSD. Hypertension is an important risk factor for cerebrovascular diseases including stroke and also have a role in the development of vascular cognitive impairment and vascular dementia. An association between hypertension and reduced blood flow and vascular dementia was documented. Studies pointed out that blood pressure levels should be kept within a certain range (below 140/90 mmHg) for prevention of cardiovascular, cerebrovascular damage and maintaining cerebral perfusion enough to preserve cognitive ability and prevention of some types of dementia. Longitudinal studies have suggested that hypertension in midlife is associated with cognitive impairment in later life.

Atrial fibrillation (AF) was frequent in patients with PSD but not significantly associated with PSD. AF does not only result in thromboembolism but also reduce cardiac output. Cardiac output reduction is greater at faster ventricular rates and could result in cerebral hypoperfusion. Failure to maintain adequate brain perfusion might be a second mechanism of brain damage and cognitive decline.

In general and consistent with the results of the present study, although IHD was more frequent in patients with PSD but had no significant association with it. This indicates greater systemic vascular damage and functional impairment in patients.

Carotid stenosis was more frequent in patients with PSD but the degree of stenosis was not significantly associated with cognitive decline. Recent studies revealed that common carotid artery intima-media thickness (CCA-IMT) predicts an increased risk for cognitive impairment, particularly poor

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**Table 5 Demographic, clinical data, vascular risk factors according to the tHcy levels**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low tHcy (≤ 12 μmol/L) (n = 59)</th>
<th>High tHcy (&gt;12 μmol/L) (n = 22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.5 ± 9.2</td>
<td>65.9 ± 10.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Males/females (n = 27/54)</td>
<td>20/39</td>
<td>7/15</td>
<td>0.554</td>
</tr>
<tr>
<td>Current smoking (n = 37)</td>
<td>17 (45.9%)</td>
<td>20 (54.1%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Hypertension (n = 33)</td>
<td>15 (45.5%)</td>
<td>18 (54.5%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Atrial fibrillation (n = 6)</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Ischemic heart disease (n = 17)</td>
<td>7 (41.1%)</td>
<td>10 (58.8%)</td>
<td>0.075</td>
</tr>
<tr>
<td>Carotid stenosis (n = 21)</td>
<td>5 (23.8%)</td>
<td>16 (76.2%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Type of stroke**

| Infarction (n = 68)           | 52 (76.5%) | 16 (20.5%) | 0.670 |
| Hemorrhage (n = 13)           | 7 (53.8%)  | 6 (46.2%)  | 0.082 |

**Size of infarction**

| Large size of infarction (n = 10) | 3 (30%) | 7 (70%) | <0.0001 |
| Small size infarctions (n = 32)   | 27 (84.4%) | 5 (15.6%) | <0.0001 |
| Lacunar infarctions (n = 26)      | 16 (61.5%) | 10 (38.5%) | 0.001   |
| Post-stroke dementia (n = 17)     | 6 (35.3%) | 11 (64.7%) | <0.0001 |

**P300 latency (delayed)**

| Large size of infarction (n = 10) | 311.05 ± 44.36 | 330.04 ± 45.50 | 0.008   |
| Small size infarctions (n = 32)   | 12 (60%)       | 8 (40%)        | 0.075   |

Notes: Data are expressed as mean ± SD and number (%); significance between low and high homocysteine levels; significance is set at p-value < 0.05.
memory and cognitive speed, in elderly women. Talelli and colleagues reported significant inverse association between the CCA-IMT and vascular cognitive decline assessed by MMSE after 12 months of ischemic stroke after adjustment for other relative risk factors. Lee and Yeh reported significant inverse association between the severity of intracranial arteries stenosis as detected by CCA-IMT and vascular cognitive decline assessed by CASI testing after three months of ischemic stroke. Severe transient attacks of ischemia as occur with carotid artery stenosis commonly result in infarction of the watershed areas present in the cerebral cortex and deep white matter. Watershed areas are most sensitive to hypoxia, but because the cortex has a lower threshold for ischemia and a higher metabolic demand, severe transient ischemia commonly results in infarction in cortical areas more readily than in deep white matter.

Although 24.7% of our patients had depression but the latter was not significantly associated with PSD. Depression is a common sequela in stroke with a reported frequency of up to 65% of all patients. Cognitive deficits could be a cause or a consequence of depression. Kimura and colleagues observed that treatment of stroke patients with nortriptyline resulted in cognitive improvement while others found the reverse.

In the present study, a significant number (27.2%) of stroke patients had elevated levels of Hcy. Compared to patients with low Hcy levels, older ages, smoking, sizable infarctions and carotid stenosis were significantly associated with higher Hcy levels. Recently, accumulating evidence from several studies suggested that raised concentrations of plasma Hcy have been associated with the risk of atherosclerosis and coronary, cerebral and peripheral vascular disease. Mild hyperhomocysteinemia (HHcy) increases in frequency from 5%–7% in the general population to 30% of patients with coronary artery disease and 42% of patients with CVS. In this study, Hcy was a risk factor of ischemic or hemorrhagic strokes, which is consistent with some studies. Boysen and colleagues found a significant difference in total Hcy levels between patients with ischemic and hemorrhagic stroke, suggesting that elevated total homocysteine is not only a reaction to acute illness but also a risk factor for recurrent stroke. Hcy has also been implicated in small vessel disease, with an increased risk of leukoaraiosis. The mechanism of HHcy-related vascular injury is a subject of much research. Dysregulation of Hcy increases the propensity for thrombosis, impaired thrombolysis, increased production of hydrogen peroxide, endothelial dysfunction and increased oxidation of low-density lipoprotein.

The relationship between Hcy and PSD is uncertain and results of different studies are conflicting. In the present study, nearly half of the patients with PSD had HHcy (47.1% compared to 22% for nondemented patients). Patients with HHcy scored lower on MMSE and CASI but involvement of any specific cognitive domain was not identified with elevated Hcy, however, delayed P300 latency of ERPs which was also significantly associated with high Hcy levels indicated poor attentional process, impaired speed of reaction and immediate memory. Cross-sectional analyses, longitudinal studies and several community-based studies showed that HHcy were significantly related to poorer performances at all neuropsychological tests. Dufouil and colleagues observed that the odds of cognitive decline was 2.8-fold (p < 0.05) higher in subjects with Hcy levels above 15 μmol/L compared with those with Hcy levels below 10 μmol/L. Seshadri and colleagues reported that increase in plasma Hcy over 14 μM double the risk of AD.

In univariate analysis, Hcy was inversely associated with age, smoking, infarction size and carotid stenosis. Prins and colleagues found that HHcy was associated with lower scores for psychomotor speed, memory function and global cognitive function in a population-based study of 1,077 nondemented elderly. In the prospective study of Folsom and colleagues, the authors found an association between smoking and HHcy and suggested that smoking may reduce vitamin B6 in the body, which is one of vitamins involved in the mechanisms for Hcy metabolism. Smoking induces depletion of cellular antioxidant and is also known to be associated with an increased Hcy level. In addition, exposure to tobacco smoke has negative impact on the folic acid level. Folic acid is cofactor by demethylation of Hcy to nontoxic methionine. Eikelboom and colleagues found a significant association between plasma Hcy levels and ischemic stroke due to large artery disease and small artery disease compared with control subjects and ischemic stroke due to cardioembolic or other etiologic subtypes of ischemic stroke. However, Hcy levels were not significantly associated with carotid stenosis. Samson and colleagues suggested that high plasma homocysteine concentrations did not play a significant role in the development of restenosis following carotid endarterectomy.

In multiple logistic regression analysis, Hcy increased the odds for cognitive impairment after adjustment of other relevant risk factors that were significantly associated with it in univariate analysis (as age, smoking, infarction size and carotid stenosis). Lehmann and colleagues found Hcy to be an independent predictor for MMSE scores in elderly persons after correcting for age, B12, and folate levels. After adjusting for age and gender but not hypertension, Sachdev and colleagues reported that high plasma Hcy
 (>12.4 μmol/l), was associated with an increased risk of developing silent brain infarctions in AD.

The results of this study and others suggested that the effect of Hcy on cognitive function is of major significance in patients with CVS, irrespective to the presence of other relevant risk factors. Direct neurotoxic effect of Hcy may be responsible for cognitive impairment in stroke patients. In support: 1) cross-sectional studies have found an inverse relationship between elevated Hcy levels and cognitive function in healthy populations;70 2) it has been recently hypothesized that cerebrovascular disease is omnipresent and the crucial role of microvascular alterations increasingly recognized in late dementia or “Alzheimer syndrome”;79 3) it has been found that elevated Hcy is associated with brain atrophy and white matter lesions;70 4) recently, HHcy in elderly patients with mental illness is found to be mainly due to concomitant vascular disease and is not related to the specific psychogeriatric diagnosis;80 and 5) the cognitive impairment is not necessarily explained by increased CVS or by lower folate or vitamin B12 levels.74

It has been found that high Hcy levels are responsible for over stimulation of the glutamate-binding site of N-methyl-D-aspartate (NMDA) receptors, which in turn promotes oxidative damage to neurons.81 Direct toxicity on glutamate neurotransmission and vascular endothelin, indirect inhibition of transmethylation reactions in brain and potentiation of amyloid neurotoxicity and promotion of tau phosphorylation are potential mechanisms of Hcy-induced cognitive dysfunction.82

The possibility that Hcy being a risk factor for cognitive impairment after stroke leads to important therapeutic implications as HHcy can be corrected with vitamin supplementation.18 HHcy linked with cognitive impairment might be an indirect marker for low concentrations of vitamin B12, vitamin B6, or folate, resulting from low intake or from an impaired transport of the vitamins to the brain. Although the levels of folic acid and Vitamin B were not evaluated in this study, however, the possibility of insufficient dietary intake due to low socioeconomic status of patients can not be excluded as cause of HHcy. Multicenter randomized trials for stroke prevention determined that vitamin B supplementation is able to reduce the incidence of recurrent vascular events in patients with stroke or transient ischemic attacks and dementia.83 Hcy-lowering treatment proved to be effective in prevention of cognitive deficits secondary to stroke and several neuropsychiatric disorders in retrospective studies. Schroocksnadel and colleagues84 documented that the use of antioxidant vitamins and anti-inflammatory drugs reduced the levels of Hcy and also the risk for vascular dementia.

The current study has some limitations: a) it did not include sufficient number of patients. It involved only a hospital-based sample; b) there were no historical dietary data; c) no evaluation for the levels of folic acid or vitamin B12 or vitamin B6 was done; and d) we did not do high resolution MRI brain scan for patients (due to the limited facilities at our hospital) as silent brain infarctions may be a confounding variable for marked and progressive cognitive decline.

Conclusions

This study indicated that cognitive decline is a common adverse consequence after CVS. Better knowledge of the risk factors for PSD should increase the effectiveness of preventive strategies for patients with stroke. A significant inverse relationship was identified between Hcy and cognition despite the presence of other relevant risk factors for stroke. It is possible that cognitive impairment may result from CVS and its related vascular risk factors including the direct association with high Hcy levels. Longer follow up studies in large sample size are necessary to determine the impact of Hcy on progression of post-stroke cognitive impairment. Because HHcy is a potentially reversible risk factor and can be identified early, prospective intervention studies should investigate whether lowering Hcy levels by vitamin supplementations could reduce the incidence and progression of cognitive decline after stroke.

Disclosure

The authors report no conflicts of interest in this work.

References


