Am J Transl Res 2021;13(3):1884-1889
www.ajtr.org /ISSN:1943-8141/AJTR0120140

Original Article

Risk factors for cognitive impairment in patients with first-time ischemic stroke

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Received August 12, 2020; Accepted September 24, 2020; Epub March 15, 2021; Published March 30, 2021

Abstract: Objective: To determine the risk factors for cognitive impairment (CI) in patients with first-time ischemic stroke. Methods: The clinical data of 180 patients with ischemic stroke who were admitted to our hospital from January 2018 to December 2019 was retrospectively analyzed. Patients with MMSE score ≤24 were included into the CI group and the rest of the patients were placed into the normal group. Multivariate logistic regression was applied to describe risk factors for CI in patients with first-time ischemic stroke. Results: Among the patients with first-time ischemic stroke, 96 cases (53%) developed CI, 84 cases (47%) were normal. In different subtypes of TOAST classifications, patients with large-artery atherosclerosis had the highest CI incidence (66.96%). For different infarction sites, the highest CI incidence occurred in the frontal lobe (82.35%), and the lowest was from cerebellar infarction (37.50%). The difference of CI incidences in the frontal lobe, parietal lobe, temporal lobe and occipital lobe was significant between the two groups (P<0.05). Logistic regression analysis indicated that independent risk factors for CI in patients with first ischemic stroke include age ≥60 years old, diabetes history, CRP >6.53 mg/L, Hcy >13.84 μmol/L, NIHSS score >4.37, VD <45.16 nmol/L, and the difference was statistically significant (*P*<0.05). Conclusion: The study showed a high CI incidence in patients with preexisting ischemic stroke. Age ≥60 years old, history of diabetes mellitus, CRP >6.53 mg/L, Hcy >13.84 μmol/L, NIHSS score >4.37 score, VD <45.16 nmol/L are independent risk factors for CI in patients with first-time ischemic stroke.

Keywords: First time ischemic stroke, cognitive impairment (CI), risk factors

Introduction

Ischemic stroke occurs when the blood supply to the brain is interrupted or reduced, and accounts for approximately 70% of all strokes. The type of ischemic stroke includes cerebral thrombosis, lacunar infarct and cerebral embolism, etc. [1, 2]. Post-stroke cognitive impairment (PSCI) refers to all forms of cognitive decline that develop within the first six months after stroke [3], encompassing all cognitive loss even if not severe enough to fit the criteria of dementia. PSCI is a common post-stroke complication, also a leading cause of disability worldwide [4], so the risk factors associated with PSCI needs to be determined. Previous studies have demonstrated a negative correlation between the level of vitamin D (VD) and the risk of ischemic stroke [5]. However, whether the level of VD is associated with PSCI still remains unclear. The study aims to determine risk factors for CI in patients with ischemic stroke, so as to provide a new insight into CI prevention and treatment. The details of this study are presented as follows.

Data collection and methods

Study subjects

The study enrolled 180 patients who were diagnosed with ischemic stroke and were admitted to our hospital from January 2018 to December 2019. The clinical data of the patients was studied retrospectively. Inclusion criteria: (1) patient who met the diagnostic criteria for ischemic stroke [6], with interval from onset to hospital admission ≤2 weeks; (2) HAMD score <7; (3) first onset; (4) complete clinical data. (5) singed an informed consent form. Exclusion criteria: (1) patient who was diagnosed with neurodegenerative dementia, or CI caused by non-vascular conditions including epilepsy, encephalitis, etc.; (2) patient who was unable to com-

municate including hearing impairment, severe aphasia or disturbance of consciousness; (3) history of mental illness. Our study obtained approval from our hospital's ethics committee.

Data collection

The study collected the following items of patient data: age, sex, history of hypertension, history of coronary heart disease, history of diabetes mellitus, history of cerebral infarction, leukoaraiosis (LA), fasting blood glucose (FBG), C-reactive protein (CRP), low-density lipoprotein-cholesterol (LDL-C), homocysteine (Hcy), VD, the National Institutes of Health stroke scale (NIHSS) score, TOAST classification in acute ischemic stroke, etc.

Study grouping

In the study, the Mini-Mental State Examination (MMSE) [6] was applied to access CI, including orientation to time and place, attention, math skills, language, instant memory, delayed memory and visual-spatial skills. The MMSE has a maximum score of 30 points, taking 5-10 min to complete. In the study, patients scoring ≤24 were included in the CI group, while the rest of the patients were placed in the normal group.

Statistical methods

The study used SPSS 25.0 software for statistical analysis. The quantitative data was expressed as (x±sd), compared with t-test. Chi-squared test was applied to compare qualitative data. Logistic regression analysis was performed for multivariate analysis. A *p*-value less than 0.05 was considered statistically significant.

Results

CI percentage in the study

In the study, patient with first-time ischemic stroke consisted of 96 (53%) cases suffering CI and 84 (47%) normal cognition patients.

Single-factor analysis for CI risk factors in patients with first-time ischemic stroke

There was no significant difference in sex, history of hypertension, history of coronary heart disease, history of cerebral infarction, LA, FBG, LDL-C between the the CI group and the normal group (P>0.05), but there was significant difference in age, history of diabetes mellitus, CRP, Hcy, NIHSS score, and VD between the two groups (P<0.05) (**Table 1**).

CI incidence in the TOAST classification

For different subtypes of the TOAST classification, patients with large-artery atherosclerosis had the highest CI incidence (66.96%) (**Table 2**).

Infarction sites and CI incidence

CI incidence in one infarction site = case number of patients developing CI in the infarction location/total cases number of patients with infarction in the location. Patients with infarction in the frontal lobe had the highest CI incidence (82.35%), and cerebellar infarction had the lowest (37.50%). The difference of CI incidences in frontal lobe, parietal lobe, temporal lobe and occipital lobe was significant between the two groups (P<0.05) (**Table 3**).

ROC curve analysis of VD and Hcy levels in predicting CI incidence

The levels of VD and Hcy indicated high sensitivity and specificity in predicting CI incidence (**Figure 1** and **Table 4**).

Multivariate analysis for CI risk factors in patients with first-time ischemic stroke

Logistic regression analysis indicated that the independent risk factors for CI in patients with first ischemic stroke include age ≥60 years, history of diabetes mellitus, CRP >6.53 mg/L, Hcy >13.84 μmol/L, NIHSS >4.37, VD <45.16 nmol/L. The difference was statistically significant (P<0.05) (**Table 5**).

Discussion

PSCI is a significant concern for stroke patients and their families. It is believed that early diagnosis for CI will offer a promising chance for early rehabilitation and follow-up treatment. As Hachinski et al. [7] argued in the *World Stroke Day Proclamation*, it is important to "incorporate the prevention of post-stroke dementia as an integral part of stroke care". In 2016, the American Stroke Association (ASA) and the American Heart Association (AHA) co-released the *Guidelines for Adult Stroke Rehabilitation*

Table 1. CI risk factors in patients with first-time ischemic stroke

Factor	CI group (n=96)	Normal group (n=84)	χ^2/t	*P*
Age (years)				
≥60	70	49		
<60	26	35	4.253	0.039
Gender (n)				
Male	46	40		
Female	50	44	0.002	0.968
Hypertension (n)				
Yes	53	43		
No	43	41	0.291	0.590
Coronary heart disease (n)				
Yes	12	10		
No	84	74	0.015	0.903
Diabetes mellitus (n)				
Yes	30	10		
No	66	74	9.700	0.002
Cerebral infarction (n)				
Yes	47	43		
No	49	41	0.089	0.765
Leukoaraiosis (LA)				
Yes	46	45		
No	50	39	0.573	0.449
FBG (mmol/L)	6.19±2.13	6.06±2.15	0.407	0.685
CRP (mg/L)	10.16±3.15	3.58±0.97	18.390	<0.001
LDL-C (mmol/L)	2.76±0.59	2.83±0.63	0.769	0.443
Hcy (μmol/L)	15.46±4.48	12.41±3.85	4.863	<0.001
NIHSS score	6.12±1.74	3.19±0.96	13.710	<0.001
VD (nmol/L)	37.45±6.42	52.89±8.62	13.730	<0.001

Table 2. CI incidence in the TOAST classification

Subtype of the TOAST Classification	Total cases (n)	Number of CI case (n)	Incidence (%)
Large-artery atherosclerosis	112	75	66.96
Small-vessel occlusion	21	4	19.05
Cardioembolism	8	2	25.00
Other defined cause	5	1	20.00
Unknown cause	34	14	41.18

and Recovery, which provided highlights for assessment of cognition and memory, etc. [8]. The study aims to determine risk factors for CI in patients with first-time stroke by patient's clinical symptoms, routine examination, MMSE scale score and so forth. The tests and examinations applied in the study are convenient for clinical operation and with good compliance in patient. The CI incidence varies according to the diagnostic criteria, assessment timing and method, ranging from 20%-80% by previous research [9, 10]. Our study found that CI incidence within 3 months after stroke was 53%, indicating that the highest CI incidence occurred in patients with large-atherosclerotic cerebral infarction, which is in line with the previous studies. The reason may be summarized as following: large-atherosclerotic cerebral infarction is associated with more severe cerebral vascular stenosis, more extensive infarc-

Table 3. CI incidence in different infarction locations

Infarction location	CI group (n=96)	Normal group (n=84)	CI incidence (%)	χ^2	*P*
Basal ganglia	31	37	45.59	2.634	0.105
Frontal lobe	42	9	82.35	24.079	<0.001
Parietal lobe	40	15	72.73	11.969	0.001
Brain stem	23	21	52.27	0.026	0.871
Temporal lobe	32	11	74.42	10.092	0.001
Occipital lobe	18	6	75.00	5.223	0.022
Cerbellum	6	10	37.50	1.769	0.184
Thalamus	4	5	44.44	0.301	0.583
Corpus callosum	3	1	75.00	0.772	0.380

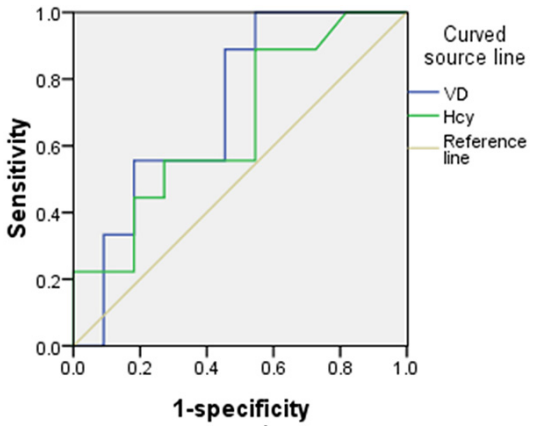

Figure 1. ROC curve of VD and Hcy levels in predicting CI incidence.

tion, and the lack of effective establishment of collateral circulation, leading to massive damage to the cortex or subcortex, which contributes to severe CI [11].

There are a number of CI-related risk factors, and studies for different factors varied in results. Our study demonstrated that independent risk factors for CI in patients with first ischemic stroke include age ≥60 years, history of diabetes mellitus, CRP >6.53 mg/L, Hcy >13.84 μmol/L, NIHSS 4.37, VD <45.16 nmol/L. Some studies have shown that age is one of the leading risk factors for dementia, also a major predictor for PSCI [12]. It is generally believed that old-age patients are more likely to develop CI [13], despite the controversial definition of old age. The older patients with stroke tend to show more fragile vessels, more severe amyliod precursor protein (APP) and higher level of total β-amyloid protein (Aβ) and Aβ42 in entorhinal cortex and hippocampal structure [14]. That is why aging is associated with CI. Other risk factors for CI involve some metabolic conditions including hyper-homocysteinemia (Hcy) and hyperglycemia. Controlling Hcy level is used to reduce the recurrence rate of stroke. Hcy, a sulfur containing amino acid, is an intermediary metabolic product derived from the metabolism of methionine (Met) to cysteine (Cys). Elevated Hcy is well recognized associated with oxidative stress, resulting in endothelial dysfunction, impaired fibrinolytic function and proliferation of vascular smooth muscle cell (VSMC) [15], as well as atherosclerosis, which are all risk factors leading to CI. Post-stroke patients with diabetes mellitus commonly experience cognitive decline. Approximately 21% of the patients included in the study had history of diabetes mellitus, which can lead to the decrease of neuron density in hippocampus area. Some studies involving rat models of ischemic stroke indicated a reduced vascular surface in the hippocampus. The Hippocampus is highly sensitive to ischemic injury since its neurons rely on constant blood flow for nutrition [16]. Also, the insulin receptor is broadly expressed in regions including the cerebral cortex and hippocampus. Insulin deficiency can cause impaired signaling pathways in the cortex and hippocampus, reduced neurotrophic Aβ but increased neurotoxic Aβ, enhanced inflammatory reactions, free-radical formation, cell damage effects, and excitatory amino acids (EAA) [17, 18]. All these changes facilitate neurofibrillary tangles, neuronal degeneration and injury [19]. From another perspective, diabetes mellitus is a chronic inflammatory condition. Over-activated inflammatory cells can further damage vascular endothelial cells and neurons, thus leading to severe cognitive loss [20]. Beyond the above factors, VD is an independent risk factor for CI in patients

Table 4. Results of ROC curve of VD and Hcy levels in predicting CI incidence

Parameter	AUC	Cut-off value	Sensitivity (%)	Specificity (%)	*P* value	95% CI	
						Lower limit (LL)	Upper limit (UL)
VD	0.717	45.16	82.21	85.47	0.024	0.486	0.948
Hcy	0.662	13.84	76.61	80.91	0.036	0.418	0.905

Table 5. Risk factors for CI in patients with first-time ischemic stroke

Factor	β	Wald χ^2	*P* Value	OR (95% CI)
Age ≥60 years	0.654	5.172	0.035	1.923 (1.124, 6.594)
History of diabetes mellitus	1.213	7.492	0.004	3.364 (2.186, 7.481)
CRP >6.53 mg/L	0.768	5.987	0.021	2.156 (1.364, 5.498)
Hcy >13.84 μmol/L	1.063	6.154	0.013	2.894 (1.654, 6.743)
NIHSS score >4.37	0.680	5.637	0.026	1.974 (1.320, 6.497)
VD <45.16 nmol/L	1.104	7.219	0.008	3.017 (2.134, 7.069)

with first-time ischemic stroke. VD deficiency and VD receptor (VDR) polymorphisms can block the binding affinity between VD and VDR [21], thus posting a cognitive decline in patients.

In conclusion, the study shows a high CI incidence in patients with preexisting ischemic stroke. The independent risk factors for CI in patients with first ischemic stroke include age ≥60 years, history of diabetes mellitus, CRP >6.53 mg/L, Hcy >13.84 μmol/L, NIHSS >4.37, and VD <45.16 nmol/L.

Acknowledgements

This research was supported by the Medical science research project of Hebei Province in 2020, No. 20200308.

Disclosure of conflict of interest

None.

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