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Original Article

Association between post-stroke depression in lacunar stroke patients and rehospitalization

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Abstract: There are few studies that explore the impact of post-stroke depression (PSD) on the rehospitalization. The aim of the study was to investigate the relationship between PSD in lacunar stroke patients and rehospitalization at 1 year. A total of 526 lacunar stroke patients admitted to hospital were observed between Jul 2011 and Jul 2016. The patients were divided into PSD group and non-PSD group according to DSM-IV criteria. All patients were followed up for 12 months. The association between post-stroke depression in lacunar stroke patients and rehospitalization was estimated. Among 526 lacunar stroke patients, 102 patients (19.3%) were PSD. After adjusting for possible confounders, patients with PSD showed a significant increase in the risk of all-cause rehospitalization (OR = 2.18, 95% CI = 1.27-3.74), vascular rehospitalization (OR = 1.95, 95% CI = 1.09-3.50) and psychological rehospitalization (OR = 2.61, 95% CI = 1.41-4.85) at 1 year compared with the patients without PSD. Post-stroke depression in lacunar stroke patients may be associated with a higher risk of all-cause rehospitalization, vascular rehospitalization and psychological rehospitalization at 1 year.

Keywords: Post-stroke depression, lacunar stroke, rehospitalization

Introduction

Lacunar stroke is a small (≤1.5 cm) infarction that accounts for approximately 25% of ischemic stroke, and 20% of all strokes [1]. Recent evidence suggests the lacunar infarction (LI) has been shown to promote depression [2]. Post-stroke depression (PSD) is one of the most common complications of cerebral vascular diseases, and its main symptoms include low mood, decreased interests, despair, anxiety, sleep disorders and somatic symptoms. Most previous studies reported depression could increase the risk of readmission in patients with stroke and other medical diagnoses [3-4]. However, there are few studies that explore the impact of PSD in lacunar stroke patients on the rehospitalization. The aim of the study was to investigate the relationship between PSD in lacunar stroke patients and rehospitalization. The study may have important implications for clinicians for improving care and prevention of PSD patients.

Methods

The study protocol was approved by the Medical Ethical Review Board of the 7th Division Hospital of Xinjiang Production and Construction Corps. Written informed consent was obtained from all participants. Between Jul 2011 and Jul 2016, consecutive 526 lacunar stroke patients were enrolled.

Subjects

Inclusion criteria were: (1) Lacunar stroke was defined as a clinical lacunar syndrome [5], with an anatomically compatible lesion on MRI or CT (≤15 mm in diameter). (2) Onset of stroke within 7 days. (3) Age 18 years or older. Exclusion criteria were: (1) Severe dementia, severe aphasia, disturbance of consciousness, or hearing loss that can not cooperate with the examiner. (2) Severe dysfunction of heart, lung, liver, or kidney. (3) Severe mental disorder. (4) Stroke history. (5) Cerebral hemorrhage, brain trauma,

or intracranial tumor. (6) Depression or antidepressant drugs history. (7) Loss of follow-up.

Diagnosis of PSD

PSD was diagnosed by DSM-IV criteria within 1 month after stroke, with at least 1 core symptom of depressed state of mind, and at least four of the following [6]: (1) Loss of interest in or no pleasant feelings about activities, (2) The loss of energy or fatigue, (3) Psychomotor retardation or agitation, (4) Feelings of worthlessness, (5) Diminished ability to think or concentrate, (6) Recurrent thoughts of death, (7) Sleep disorders such as insomnia or sleeping too much, and (8) Significant weight loss or weight gain. The symptoms must have lasted for at least 2 weeks and cannot be due to substances or organic mental disorder.

Clinical data collection

The general information was recorded for all participants at admission: age, sex, smoking, drinking, weight and height, and history of hypertension, diabetes mellitus, cardiac disease and stroke. Within 24 hours after admission, stroke severity was assessed according to the National Institutes of Health Stroke Scale (NIHSS). The next day an overnight fasting venous blood sample was taken to determine glucose and lipid levels. Locations of lacunar infarcts were detected by brain MRI or CT.

Hypertension was diagnosed at least one of the following: (1) History of Hypertension, (2) Using anti-hypertension drugs, and (3) The mean of 3 measurements of systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg. Diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association [7]. Hyperlipidemia was defined as history of hyperlipidemia or TC > 5.72 mmol/L and (or) TG > 1.7 mmol/L. Drug therapy included intravenous thrombolysis, anti-coagulation, anti-platelet, anti-hypertension, lipid lowering drug, anti-hyperglycemic drug and anti-depressant drugs.

Follow-up data

All participants were followed up by telephone or outpatient visit every three months. The follow-up period was 1 year. We considered rehospitalization to have occurred when a patient was readmitted to a medical unit within one-year period following the admission to the hospital for stroke. All-cause rehospitalization was divided into vascular rehospitalization, psychological rehospitalization and other. Vascular rehospitalization was divided into vascular events (vascular death, stroke recurrent, and myocardial infract) and vascular ischemia (TIA, vertebrobasilar insufficiency, angina). Vascular ischemia was defined as ischemia of cerebral vessels or coronary artery, and the examination results showing no infarction or hemorrhage.

Statistic analysis

Categorical data are presented as numbers (percentage), Chi-square analyses were used for comparison. Continuous variables fitting normal distribution were expressed as mean ± standard deviation, t-test was used. Continuous variables not fitting normal distribution were expressed as median (interquartile range), Mann-Whitney U-test was used. Univariate Logistic regression analysis was used for the assessment of the correlation between PSD and rehospitalization. Multivariate logistic regression was used to estimate adjusted odds ratios (ORs) and its 95% CI for associations of PSD and rehospitalization. Associations were adjusted for age and gender in Model 1. In Model 2, we adjusted for age, gender, BMI, smoking, drinking, hypertension, diabetes, cardiac disease, hyperlipidemia, NIHSS, anti-platelet, lower lipid drug, and anti-depressant drug. Bilateral $P<0.05$ represented a significant difference. The statistical analyses were performed by the SPSS 17.0 software.

Results

A total of 526 patients were included in the study after excluding those who were lost to follow-up. Among a total of 526 patients, 102 patients (19.3%) were PSD. Baseline characteristics of PSD and Non-PSD are presented in **Table 1**. There were significant differences between the two groups in gender and antidepressant drugs ($p<0.05$). The follow-up data are presented in **Table 2**. There were significant differences between the two groups in all-cause rehospitalization, vascular rehospitalization, psychological rehospitalization ($p<0.05$). There were significant differences between the two groups in vascular ischemia of vascular rehospitalization ($p<0.05$).

Table 1. Baseline characteristics of PSD and Non-PSD

Characteristics	PSD (n = 102)	Non-PSD (n = 424)	*P*
Age, y, mean ± SD[1]	66.73±6.28	67.49±6.41	0.19
Femal, n (%)[2]	42 (41.2)	130 (30.7)	0.04*
BMI (kg/m^2)[1]	24.35±3.21	23.78±3.05	0.12
Hypertension, n (%)[2]	65(63.7)	237 (55.9)	0.15
Diabetesmellitus n (%)[2]	23 (25.0)	88 (20.8)	0.37
Cardiac disease, n (%)[2]	18 (13.7)	50 (11.8)	0.59
Smoking, n (%)[2]	34 (33.3)	139 (32.8)	0.92
Drinking, n (%)[2]	20 (19.6)	92 (21.7)	0.64
Hyperlipidemia, n (%)[2]	30 (29.4)	123 (29.0)	0.94
Lesion Location[2]			
BG/IC	34 (33.3)	135 (31.8)	0.77
CR/centrum semiovale	26 (25.5)	113 (26.7	0.81
Thalamus	28 (27.5)	96 (22.6)	0.30
Brain trem/cerebellum	14 (13.8)	80 (19.5)	0.22
NIHSS[3]	3 (2-4)	3 (2-4)	0.35
Intravenous thrombolysis[2]	3 (2.9)	10 (2.4)	0.73
Anti-platelet[2]	88 (86.3)	373 (88.0)	0.64
Anti-coagulation[2]	9 (8.8)	21 (5.0)	0.13
Anti-hypertension[2]	51 (50.0)	190 (44.8)	0.35
Lower blood glucose drug[2]	20 (19.6)	79 (18.6)	0.82
Lower lipid drug[2]	90 (88.2)	377 (88.9)	0.85
Anti-depressant drugs[2]	12 (11.8)	8 (1.9)	0.00*

Abbreviations: BG = basal ganglia; IC = internal capsule; CR = corona radiate; [1]*t*-Test; [2]Chi-square; [3]Mann-Whitney *U* test; **P*<0.05.

Table 2. Comparison of rehospitalization between PSD and Non-PSD

Characteristics	PSD (n = 102)	Non-PSD (n = 424)	*P*
All-cause rehospitalization	47 (46.1)	114 (26.9)	0.00*
Vascular rehospitalization	20 (19.6)	51 (12.0)	0.04*
Psychological rehospitalization	22 (21.6)	48 (11.3)	0.01*
Vascular rehospitalization			
Vascular events	7 (6.9)	22 (5.2)	0.51
Vascular ischemia	13 (12.7)	29 (6.8)	0.05*

**P*<0.05.

The results from the logistic regression analyses are presented in **Table 3**. After adjustment for age, gender, BMI, smoking, drinking, hypertension, diabetes, cardiac disease, hyperlipidemia, NIHSS, anti-platelet, lower lipid drug and anti-depressant drug, multivariate regression analysis showed that patients with PSD had a significant increase in the risk of all-cause rehospitalization (OR = 2.18, 95% CI = 1.27-3.74), vascular rehospitalization (OR = 1.95, 95% CI = 1.09-3.50), and psychological rehospitalization (OR = 2.61, 95% CI = 1.41-4.85) at 1 year compared with patients without PSD.

Discussion

Factors causing depressive symptoms in cerebral small vessel disease remain uncertain. A biological mechanism has proposed that disruption of cortical-subcortical circuits can result in depression [8]. Recent studies have shown more than one-third of stroke survivors in the aftermath of an ischemic stroke experience depressive symptoms, but the prevalence of depression in the lacunar stroke patients is unclear [9]. In our study of 526 patients with lacunar infarcts, 19.3% of the participants were diagnosed PSD by DSM-IV criteria in a month. The lower incidence of PSD may be due to the selection of patients with mild stroke. Prior studies have revealed that the patients with more severe neurological impairment were more likely to be depressed [10]. Comparison of baseline characteristics of PSD and Non-PSD, the two groups were similar except that the PSD group had a significantly higher proportion of female and anti-depressant drugs. The results were consistent with other studies that have shown that female patients were more prone to develop post-stroke depression [11].

In this study the rehospitalization rate was 46.1% in PSD, significantly higher than the non-PSD group of 26.9% at 1 year. PSD was associated with a higher risk of rehospitalization. Our study results were consistent with other studies that have shown that depression can increase rehospitalizations in patients with stroke [12]. Even in other diseases, depression can also increase the readmission rate [13, 14]. When the causes of rehospitalization were distinguished, vascular and psychological factors accounted for the main reasons. We found that the odds of vascular rehospitalization at 1 year were 1.95 times

Table 3. Univariate and multivariates regression analysis for rehospitalization to PSD

Characteristics	OR (95% CI)					
	Unadjusted		Model 1		Model 2	
All-cause rehospitalization	2.30 (1.47-3.58)	0.000	2.23 (1.43-3.48)	0.000	2.18 (1.27-3.74)	0.001
Vascular rehospitalization	1.90 (1.08-3.33)	0.035	1.87 (1.06-3.29)	0.037	1.95 (1.09-3.50)	0.032
Psychological rehospitalization	2.44 (1.38-3.30)	0.002	2.37 (1.33-4.16)	0.003	2.61 (1.41-4.85)	0.002
Vascular rehospitalization						
Vascular events	1.35 (0.60-3.24)	0.507	1.35 (0.56-3.27)	0.505	1.22 (0.48-3.07)	0.675
Vascular ischemia	1.99 (0.99-3.98)	0.056	1.89 (0.94-3.80)	0.070	1.96 (0.96-3.99)	0.068

CI = confidence interval. OR = Odds Ratio. Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, BMI, smoking, Drinking, hypertension, diabetes, Cardiac disease, hyperlipidemia, NIHSS, anti-platelet, lower lipid drug, anti-depressant drug.

greater in patients with PSD than those without PSD. The underlying mechanism may be as follows: (1) One explanation for our findings could be that anxiety and depression of PSD patients may lead to unstability of blood pressure and blood glucose, which could result in adverse prognosis. (2) PSD patients often have sleep disorders, which could lead to poor efficacy of antihypertensive drugs. Poorly controlled hypertension further aggravates vascular damage. (3) PSD patients may not adhere to cardio-cerebro vascular disease prevention and treatment regimens [15]. (4) Depression may increase platelet activation and inflammatory processes [16]. (5) Autonomic nervous system dysregulation caused by depression may affect the cardiac system [17]. (6) The participants had cardiovascular and cerebrovascular risk factors. The combination of depression and vascular risk factors may contribute to higher risk of vascular rehospitalization.

Vascular rehospitalization was subdivided into vascular ischemia and vascular events. Though the PSD group had a marginally significantly higher proportion of vascular ischemia of vascular rehospitalization, non obvious correlation was found. PSD was not correlation with vascular events at 1 year. Recent studies have shown patients with PSD have poor prognosis including reduced quality of life and increased mortality, and even higher risk of recurrent stroke [18-20]. These studies were not partly consistent with our study results. However, in contrast to our choice of lacunar stroke, they selected all types of stroke patients to observe. A research has shown mood problems increase the risk of mortality in patients with lacunar infarcts during 6 years follow-up [21]. The other study has not shown an obvious correlation between depression and stroke recurrent [22]. The differences may be due to preventive treatment, as well as the number of cases and the time of follow-up.

In the present study, we observed that post-stroke depression in patients with lacunar stroke significantly increased the risk of psychological rehospitalization. After relevant examinations, new organic disease was not found in these rehospitalized patients for psychological reasons. However, through a number of psychological tests, anxiety, depression and other emotional problems were found in these patients. Research reveals stroke itself may bring about changes of neurotransmitters, which lead to emotional changes [23]. The factors including neurological impairment, fear of stroke recurrence, unilateral cognition, anxiety of therapeutic effects and so on may cause psychological problems. Of the consecutive 526 patients with lacunar infarcts, the rate of psychological rehospitalization was 13.3%. The primary symptoms of psychological rehospitalization were suspected stoke recurrence, dizziness and headache, palpitate, chest tightness and so on. Patients with psychological problems generally manifest physical discomfort, which makes it hard to distinguish. Therefore, it is not difficult to understand that PSD patients are more likely to be rehospitalized because of psychological problems.

Therefore, PSD patients should be given more attention, more psychological guidance and psychological intervention cooperating with the family. Clinicians need to be alert to the risks of rehospitalization for PSD patients, and need to explore measures to prevent readmissions [12]. Reducing avoidable hospital readmissions

can help to reduce medical expenses and alleviate the burden of society and family.

In this study, we selected lacunar stroke patients and excluded patients with heavier cerebral infarction which may influence prognosis. All participants were easy to follow up because of their mild neurologic impairment. However, the study had several limitations. This was a single-center study, sample size was limited. This study did not bring in the factors of intracranial and extracranial large artery stenosis or occlusion, which could have an impact on the results. The other factors such as economic income, family support, medical insurance policy and so on could have impacts on the results. Further research is needed to bring in more factors to investigate. The clinical and follow-up data were collected by self-reported questionnaires, which could lead to information bias.

The lacunar infarcts patients with PSD may need additional psychological intervention, which may helps to reduce rehospitalization.

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Disclosure of conflict of interest

None.

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References

[1] Sudlow CL and Warlow CP. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. Stroke 1997; 28: 491-499.

[2] Santos M, Gold G, Kovari E, Herrmann FR, Bozikas VP, Bouras C and Giannakopoulos P. Differential impact of lacunes and microvascular lesions on poststroke depression. Stroke 2009; 40: 3557-3562.

[3] Kartha A, Anthony D, Manasseh CS, Greenwald JL, Chetty VK, Burgess JF, Culpepper L and Jack BW. Depression is a risk factor for rehospitalization in medical inpatients. Prim Care Companion J Clin Psychiatry 2007; 9: 256-262.

[4] Sayers SL, Hanrahan N, Kutney A, Clarke SP, Reis BF and Riegel B. Psychiatric comorbidity and greater hospitalization risk, longer length of stay, and higher hospitalization costs in older adults with heart failure. J Am Geriatr Soc 2007; 55: 1585-1591.

[5] Traylor M, Bevan S, Baron JC, Hassan A, Lewis CM and Markus HS. Genetic architecture of lacunar stroke. Stroke 2015; 46: 2407-2412.

[6] Yang SR, Hua P, Shang XY, Hu R, Mo XE, Pan XP. Predictors of early post ischemic stroke apathy and depression: a cross-sectional study. BMC Psychiatry 2013; 13: 164.

[7] American diabetes association: clinical practice recommendations 1997. Diabetes Care 1997; 20: S1-S70.

[8] Brookes RL, Willis TA, Patel B, Morris RG and Markus HS. Depressive symptoms as a predictor of quality of life in cerebral small vessel disease, acting independently of disability; a study in both sporadic small vessel disease and CADASIL. Int J Stroke 2013; 8: 510-517.

[9] Egeto P, Fischer CE, Ismail Z, Smith EE and Schweizer TA. Lacunar stroke, deep white matter disease and depression: a meta-analysis. Int Psychogeriatr 2014; 26: 1101-1109.

[10] Loubinoux I, Kronenberg G, Endres M, Schumann-Bard P, Freret T, Filipkowski RK, Kaczmarek L and Popa-Wagner A. Post-stroke depression: mechanisms, translation and therapy. J Cell Mol Med 2012; 16: 1961-1969.

[11] Hackett ML and Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. Stroke 2005; 36: 2296-2301.

[12] Dossa A, Glickman ME, Berlowitz D. Association between mental health conditions and rehospitalization, mortality, and functional outcomes in patients with stroke following inpatient rehabilitation. BMC Health Services Research 2011; 11: 311.

[13] Kartha A, Anthony D, Manasseh CS, Greenwald JL, Chetty VK, Burgess JF Jr, Culpepper L and Jack BW. Depression is a risk factor for rehospitalization in medical inpatients. Prim Care Companion J Clin Psychiatry 2007; 9: 256-262.

[14] Jiang W, Alexander J, Christopher E, Kuchibhatla M, Gaulden LH, Cuffe MS, Blazing MA, Davenport C, Califf RM, Krishnan RR, O'Connor CM. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. Arch Intern Med 2001; 161: 1849-1856.

[15] Carney R, Freedland KE, Eisen SA, Rich MW and Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. Health Psychol 1995; 14: 88-90.

[16] Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E and Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment

resistant depression. Cytokine 1997; 9: 853-858.
[17] Kim CK, McGorray SP, Bartholomew BA, Marsh M, Dicken T, Wassertheil-Smoller S, Curb JD, Oberman A, Hsia J, Gardin J, Wong ND, Barton B, McMahon RP and Sheps D. Depressive symptoms and heart rate variability in postmenopausal women. Arch Intern Med 2005; 165: 1239-1244.
[18] Zhang WN, Pan YH, Wang XY, Zhao Y. A prospective study of the incidence and correlated factors of post-stroke depression in China. PLoS One 2013; 8: e78981.
[19] Almeida OP and Xiao J. Mortality associated with incident mental health disorders after stroke. Aust N Z J Psychiatry 2007; 41: 274-281.
[20] Yuan HW, Wang CX, Zhang N, Bai Y, Shi YZ, Zhou Y, Wang YL, Zhang T, Zhou J, Yu X, Sun XY, Liu ZR, Zhao XQ, Wang YJ. Poststroke depression and risk of recurrent stroke at 1 year in a Chinese cohort study. PLoS One 2012; 7: e46906.
[21] Grool AM, van der Graaf Y, Mali WP, Witkamp TD, Vincken KL, Geerlings MI; SMART Study Group. Mood problems increase the risk of mortality in patients with lacunar infarcts: the SMART-MR study. Psychosom Med 2012; 74: 234-240.
[22] Ellis C, Zhao Y and Egede LE. Depression and increased risk of death in adults with stroke. J Psychosom Res 2010; 68: 545-551.
[23] Loubinoux I, Kronenberg G, Endres M, Schumann-Bard P, Freret T, Filipkowski RK, Kaczmarek L and Popa-Wagner A. Post-stroke depression: mechanisms, translation and therapy. J Cell Mol Med 2012; 16: 1961-1969.