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RESEARCH ARTICLE

# Associated factors of early neurological deterioration in isolated acute lacunar infarction in basal ganglia

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brain ischemic tolerance;  
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## ABSTRACT

**Objective:** To investigate, in basal ganglia, the factors associated with early neurological deterioration (END) of isolated acute lacunar infarction.

**Methods:** 167 patients, in the retrospective group, with isolated acute lacunar infarction in basal ganglia, were defined by magnetic resonance imaging (MRI). The National Institutes of Health Stroke Scale (NIHSS) defined early neurological deterioration as increases of  $\geq 2$  within 72 hours following admission. Baseline variables predicting END were investigated with multivariate logistic regression analysis.

**Results:** In the study, END occurred in 42 (25.15%) patients. Lesions located in posterior limb of internal capsule were independent risk factors for END ( $P < 0.01$ ). Associated with END were the age of onset, history of cerebral infarction, history of diabetes, systolic blood pressure at admission and lesions of cerebral white matter. This presented significant differences ( $P < 0.05$ ). With or without diabetes and different lesion location at varying layers and inter-layers, single-factor and multi-factor analysis revealed no effect on the association between positive ENT and age, history of stroke, white matter. Previous history of stroke, pathological changes of white matter, and age of onset, correlates with END which showed significant difference ( $P < 0.05$ ).

**Conclusions:** There is a close relationship between the lesion location and other related factors, such as lesions of cerebral white matter, history of cerebral infarction, history of diabetes and age, etc. and END in patients with isolated acute lacunar infarction in basal ganglia. Protective factors of END included age  $\geq 65$ , high systolic pressure, stroke history, cerebral white matter lesions in our study.

## 1 Introduction

In 20%~30% of patients with unilateral isolated basal ganglia lacunar infarction, early neurological deterioration (END) occurs. It leads to one of the main causes for poor prognosis, post stroke, and END may progress to severe disability within several hours or days [1, 2]. The basal ganglia region is vascularized by anterior choroidal artery (AChA), internal capsule-striatum artery, and thalamo-geniculate artery. The majority of studies showed that perforating branches atherosclerosis or hypoperfusion results in END. In this study, we

focused on other possible factors that cause deterioration of neurological function and probed into the mechanisms by excluding patients with internal carotid artery and the ipsilateral middle cerebral artery stenosis.

## 2 Methods

### 2.1 Patients

In this study, the data of 167 patients suffering from unilateral isolated basal ganglia lacunar cerebral infarction, between July 2012 and June 2015, were

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retrospectively reviewed at the Department of Neurology at the Affiliated Weihai Center Hospital. Within 24 h after admission, magnetic resonance imaging (MRI), diffusion weighted imaging (DWI) and magnetic resonance angiography (MRA) confirmed their diagnoses. MRI, MRA and neck and/or intracranial vascular examination were performed, according to the standard of *Chinese Acute Ischemic Stroke Treatment Guidelines* (2010 version). Exclusion in this study were those patients with lesions extended to the body of the lateral ventricle, cortex, and centrum semiovale. Based on the trial of ORG 10172 in acute stroke treatment (TOAST) classification [3], those patients with internal carotid artery and the ipsilateral middle cerebral artery stenosis, were also excluded. Through the application and indication of DWI, patients with acute multi-lacunar infarction, bilateral cortex and subcortex acunar infarction were excluded. In addition, patients who were also excluded with lateral ventriculitis, tumor, demyelinating diseases, neural function loss caused by previous stroke history and acute cerebral infarction outside the paraventricular region. According to the National Institutes of Health Stroke Scale (NIHSS) score, END-positive patients were defined as who with increased NIHSS score  $\geq 2$  within 72 h after admission. Composed of 42 patients was the END-positive group, while the other 125 patients made up the END-negative group.

## 2.2 Method

### 2.2.1 General information

Detailed records of patients were collected, including age, gender, previous medical history (including high blood pressure, diabetes, stroke history), and individual history (smoking and drinking history). As well, the period from onset time to admission time, duration until peak, main laboratory index (admission blood glucose concentration, hemoglobin A1c reading, total cholesterol, triglyceride levels, low-density lipoproteins, coagulation function, C-reactive protein, uric acid, homocysteine), 12-lead electrocardiogram (ECG), echocardiogram, cervical vascular color ultrasonic and transcranial Doppler (TCD) exam were also collected.

### 2.2.2 Image examination

Those patients having given informed consent were

examined using 1.5 T (Signa 1.5 T, General Electric, USA) or 3.0 T (MAGENTOM 3.0 T, Siemens, Germany) MRI system. The MRI examination included T1-weighted imaging, T2-weighted imaging, diffusion-weighted imaging, fluid-attenuated inversion recovery pulse sequence and MRA. The infarctions were divided into ventral, medial or dorsal types based on axial scans including three front-to-back periventricular anatomic planes that, in turn, were based on major sites of infarction in scans of the periventricular body. Whether the infarction has extended to the radial posterior lateral ventricle was investigated using T2-weighted imaging (or DWI). Intracranial vascular examinations were completed by MRI, or head and neck CT angiography.

### 2.2.3 Clinical assessments

Initial stroke severity was measured using the NIHSS on admission. The NIHSS assessments were carried out on day 3, 7 and 14 after admission and conducted twice a day (in the morning and the afternoon) by the same doctor. The highest score on each day was then recorded. An increase of NIHSS score  $\geq 2$  within 1 week [4] was defined as END. The doctor who measured the NIHSS score in this single-blind test had no knowledge of the imaging findings of the patients.

## 2.3 Statistical analysis

Statistical Package for Social Sciences software (SPSS 16.0; IBM, Armonk, New York) was used to analyze the data. Quantitative data in non-normal distribution were indicated with medians and quartiles, while quantitative data in normal distribution were expressed as  $\bar{x} \pm s$ . Independent sample *t*-test was employed for comparison between the two groups. The two groups were compared using the  $\chi^2$ -test and Fisher's exact test, and ranked data were expressed as percentages. Variables with  $P < 0.1$  were exclusively included in the logistic model to analyze the effects of END-predicting factors and adjusted confounders, as determined in univariate analyses. Differences in age, gender and lesion location (posterior limb of internal capsule, posterior part of periventricle and corona radiata area) were analyzed separately in patient subgroups. Statistically significant was defined as  $P < 0.05$ .

### 3 Results

Among the 167 patients with cerebral infarction, 42 showed early neurological deterioration (END-positive), while 125 did not (END-negative). Patients with high incidence ( $P < 0.05$ ) (Table 1) of END were under the age of 65, whose dorsal parts of periventricle area were involved, and had lower systolic blood pressure, higher C-reactive protein and admission blood glucose level, but had no history of stroke and leukoencephalopathy.

Stepwise logistic regression to analyze the possible related factors in END-positive patients ( $\alpha_E = 0.05$ ,  $\alpha_R = 0.10$ ) was performed. Results indicated protective factors of END (OR value: 0.831, 0.569, 0.797, 0.963,

respectively,  $P < 0.05$ ) occurred for those patients over 65 years old, who had higher systolic blood pressure, history of stroke, and leukoencephalopathy. On admission, dorsal infarction and higher level of blood glucose were independent risk factors for END (OR value are 4.687 and 1.531, respectively,  $P < 0.05$ ) (Table 2).

We analyzed related univariate and multivariate to END by hierarchical regression based on the presence of diabetes and different positions of lacuna infarctions, because diabetes history and the varying positions of lacunar infarctions could be the confounding factors of age, stroke history and white matter lesions. Results indicated that diabetes mellitus and different positions of lacunar infarctions did not affect the positive correlation between END-positive and age, history of

**Table 1** General information of END positive and negative patients.

Variable		END negative	END positive	$t/\chi^2$ value	$P$ value
Age	< 65	45 (66.18%)	23 (33.82%)	4.584	0.032
	≥ 65	80 (80.81%)	19 (19.19%)		
Gender	Male	67 (72.83%)	25 (27.17%)	0.446	0.504
	Female	58 (77.33%)	17 (22.67%)		
NIHSS score at admission	—	1.96 ± 0.57	2.08 ± 0.45	1.245	0.217
Site of infarction	Ventral	28 (82.35%)	6 (17.65%)	6.969	0.031
	Medial	43 (83.31%)	8 (15.69%)		
	Dorsal	54 (65.85%)	28 (34.15%)		
Systolic blood pressure (mmHg)	—	149.32 ± 15.41	143.68 ± 14.89	-2.078	0.040
Diastolic blood pressure (mmHg)	—	83.97 ± 11.12	85.49 ± 9.97	0.792	0.433
Hypertension	No	34 (79.07%)	9 (20.93%)	0.548	0.459
	Yes	91 (73.39%)	33 (26.61%)		
Diabetes mellitus (DM)	No	90 (73.77%)	32 (26.23%)	0.280	0.596
	Yes	35 (77.78%)	10 (22.22%)		
Ever smoker	No	77 (74.76%)	26 (25.24%)	0.348	0.555
	Yes	38 (70.37%)	16 (29.63%)		
Alcohol drinking	No	54 (76.06%)	17 (23.94%)	0.095	0.757
	Yes	71 (73.96%)	25 (26.04%)		
History of stroke	No	76 (69.09%)	34 (30.91%)	5.679	0.017
	Yes	49 (85.96%)	8 (14.04%)		
Homocysteine (μmol/L)	—	9.12 ± 2.89	9.67 ± 2.56	1.097	0.274
High density lipoprotein cholesterol (mmol/L)	—	1.18 ± 0.20	1.22 ± 0.17	1.172	0.246
Low-density lipoproteins (mmol/L)	—	2.68 ± 0.74	2.57 ± 0.82	-0.815	0.419
Serum creatinine (mmol/L)	—	72.69 ± 20.86	73.83 ± 19.71	0.318	0.757
Serum uric acid (mmol/L)	—	319.15 ± 78.23	311.70 ± 86.26	-0.527	0.604
C-reactive protein (mmol/L)	—	0.98 ± 0.18	1.13 ± 0.21	4.482	< 0.001
Admission blood glucose (mmol/L)	—	6.35 ± 2.17	7.34 ± 2.26	2.534	0.012
Leukoencephalopathy	No	72 (67.92%)	34 (32.08%)	7.394	0.007
	Yes	53 (86.89%)	8 (13.11%)		

**Table 2** Multivariate logistic regression analyses of significant risk factors for END.

Variable	$\beta$	SE	Wald	P value	OR value	95% CI
Age <sup>a</sup>	-0.672	0.255	8.637	0.026	0.831	0.422~0.950
Site of infarction	—	—	9.085	0.006	—	—
Medial <sup>b</sup>	0.6334	0.439	5.532	0.172	1.224	0.834~1.926
Dorsal <sup>b</sup>	2.598	0.826	12.089	0.001	4.687	2.185~12.239
Systolic blood pressure	-0.286	0.097	6.903	0.042	0.569	0.334~0.8892
History of stroke	-1.235	0.338	8.531	0.026	0.797	0.598~0.964
C-reactive protein	0.582	0.115	4.064	0.285	1.003	0.851~1.461
Admission blood glucose	0.339	0.082	8.012	0.024	1.531	1.143~1.982
Leukoencephalopathy <sup>c</sup>	-1.539	0.673	10.137	0.003	0.963	0.885~0.997

a, age<65 as reference criterion; b, ventral infarction as reference criterion; c, without leukoencephalopathy as reference criterion.

stroke or leukoencephalopathy (Table 3).

#### 4 Discussions

A common ischemic stroke in deep brain regions featured by high END incidence rate and disability rate is basal ganglia lacunar stroke. Further neuro-functional injury can occur rapidly and peak in 3~5 days even though it begins with a mild nerve function deficit. The curative effect and prognosis were limited by the narrow thrombolysis treatment time-windows. The fact that perforating arterial

occlusions play a crucial role in basal ganglia lacunar stroke is currently widely accepted. Nevertheless, radiological examinations rarely found lesions at the perforating artery; even digital subtraction angiography (DSA) exams are unable to identify carotid artery stenosis or perforating artery occlusion [1]. Low perfusion watershed infarction, as suggested by other studies, could contribute its pathogenesis. In addition, lenticulostriate artery lesion, middle cerebral artery stenosis or Heubner recurrent artery stenosis may be involved [5, 6]. Basal ganglia lacunar stroke related risk factors, based on the administered patients from

**Table 3** The correlation between END positive and age, stroke history or leukoencephalopathy.

Variable	Age		Stroke history		Leukoencephalopathy		
	$\geq 65$	$< 65$	With	Without	With	Without	
DM	NO <sup>a</sup>	0.892 (0.334~0.926)	1.384 (1.029~2.671)	0.764 (0.589~0.897)	1.183 (1.002~1.639)	0.808 (0.773~0.934)	1.205 (1.137~1.689)
	YES <sup>b</sup>	0.711 (0.389~0.871)	1.038 (1.071~2.394)	0.708 (0.435~0.826)	1.267 (1.317~1.925)	0.724 (0.539~0.894)	1.178 (1.089~2.006)
SI	Ventral <sup>c</sup>	0.734 (0.689~1.832)	1.591 (1.257~2.039)	0.938 (0.572~0.985)	1.083 (1.061~2.192)	0.831 (0.702~0.929)	1.282 (1.029~1.591)
	Medial <sup>d</sup>	0.972 (0.681~0.994)	1.432 (1.115~2.447)	0.793 (0.618~0.906)	1.256 (1.097~2.058)	0.794 (0.605~0.883)	1.539 (1.373~1.992)
	Dorsal <sup>e</sup>	0.989 (0.683~0.998)	2.385 (1.639~4.159)	0.893 (0.694~0.949)	3.281 (1.773~5.201)	0.835 (0.772~0.972)	2.338 (1.524~4.384)

DM: diabetes mellitus; SI: site of infarction.

In each regression model, the adjusted independent variables were composed of variables which were statistically significant ( $P < 0.1$ ) in the stratified univariate analysis. a, adjusted for NIHSS score at admission, SI, C-reactive protein and admission blood glucose concentration; b, adjusted for NIHSS score at admission, SI, systolic blood pressure, ever smoker, low-density lipoproteins concentration, C-reactive protein and admission blood glucose concentration; c, adjusted for NIHSS score at admission, systolic blood pressure, hypertension, DM, high-density lipoprotein cholesterol concentration, low-density lipoproteins and C-reactive protein concentration; d, adjusted for gender, NIHSS score at admission, systolic blood pressure, hypertension, DM, high-density lipoprotein cholesterol concentration, C-reactive protein and admission blood glucose concentration; e, adjusted for NIHSS score at admission, systolic blood pressure, DM, C-reactive protein and admission blood glucose concentration.

the past two years, were analyzed in this retrospective study. We assessed NIHSS score to identify END positive patients after excluding large-artery atherosclerosis diagnosis. An END incident rate around 10% ~ 40% was found in previous studies [7]. Our END data showed the incident rate is 25.15%, which is consistent with the previous reports. The incidence of our study generated a lower percentage than in previous studies because the large-artery atherosclerosis patients were excluded, which reduced the study sample size.

Moreover, we also found a significant correlation between END and lesion location, age, white matter lesions, history of stroke or diabetes, and systolic blood pressure on hospital admission. In addition, posterior lateral ventricle lesions are significantly correlated to END ( $P < 0.01$ ). The history of diabetes and systolic blood pressure on admission is associated with END as well ( $P < 0.05$ ), which is consistent with the previous studies [8]. Contrary to previous studies, which reported no correlation between white matter lesions classification and lacunar cerebral infarction induced END [9], our research suggested that the protective factors in lacunar stroke include history of stroke, white matter lesions and age. A brain ischemia tolerance after lacunar stroke may be activated by the protective factors.

The body's ability to tolerate against cerebral ischemia events is called brain ischemia tolerance. Related protection mechanisms can be activated and protect ensuing ischemic injury, which reduce lesion volume, and alleviate neural function impairment after cerebral blood reperfusion. Included in these mechanisms are two endogenous protective strategies: ischemic preconditioning (IP) and ischemic postconditioning (IPC). IP, an earlier proposed neural protective strategy that occurs after subconscious stimulus and before harmful ischemia, can be divided into two stages: the rapid pretreatment (3 ~ 5 min after the preconditioning stimulus, after 1 h), and delayed preconditioning (start after 2~3 d pretreatment, after 1 week). Extremely complicated, neural protective mechanisms in IP are involved with many gene expressional regulations and signal transduction pathways. IPC is the other endogenous protective strategy, which is recently discovered, induces ischemia tolerance in target organs to reduce ischemia-

reperfusion injury and protect normal function. To date, it is not fully clear what the mechanism is for novel neural protection strategy to induce brain ischemia tolerance. The transient whole-brain or partial-brain region ischemia, as being revealed through a number of pre-clinical experiments, showed neural-protective functions in severe ischemia even following a specific time interval to ischemia stimulation [10, 11]. Patients with history of transient ischemic attack (TIA) equivalent are also experiencing IP, which may belong to IPC. Clinical study indicated that TIA would affect re-ischemia by two main approaches: cumulative damage and protective tolerance. As well, other studies have also demonstrated that if two ischemia episodes occur continuously in a few hours, the second ischemia episode would aggravate the first one; this is known as cumulative damage. IP is observed to be activated and protect against lethal re-ischemia, if the time interval between two ischemia episodes is extended [12]. Indeed, patients with longer interval between TIA and infarction, as observed by Caplan et al. [13], were proved to have a better prognosis vs. patients without prior TIA or with short interval. This finding suggested an ischemic tolerance effect in neural protection function.

Partially similar to natural adaptation mechanisms were the characteristics of brain ischemia tolerance. The history of cerebral infarction in patients and cerebral white matter lesions was investigated in this study. A small vascular lesion induced by chronic ischemia might be suggested by cerebral white matter lesions. An endogenous protective mechanism for protective tolerance may be activated by these factors. A high incidence of chronic hypoperfusion, which is a feature of leukoencephalopathy, in small vascular lesions was exhibited on hypertension patients. The low microcirculatory perfusion status before infarction possibly activates IP and leads to gene expression regulation and cell defense mechanism strengthening against acute ischemia. This might play a significant role in early neurologic protection and prevent disease progression from worsening [14, 15]. In addition, having less capacity to tolerate stroke attack, younger patients present a more severe impairment compared to elderly patients. Still, other neural regulation mechanisms may be involved for later neural function rehabilitation. Therefore, significant indicators for early

neurologic deterioration may include age, history of cerebral infarction, and cerebral white matter lesions.

Protective factors of END included age  $\geq 65$ , high systolic pressure, stroke history, cerebral white matter lesions in our study. In basal ganglia lacunar stroke patients, ischemia intolerance is the main mechanism of END. Perhaps more importantly, repeated IP and ICP may be induced by prior cerebral infarction or cerebral white matter lesions. This, in turn, could activate endogenous protective mechanisms, thereby promotes the establishment of collateral circulation and enhances the ability to fight against subsequent ischemic events at last. Currently, many IP methods such as hyperbaric oxygen and electric acupuncture, which enhance cerebral ischemia tolerance have been employed [16, 17]. Although these approaches are proved to be effective in animal experiments, the mechanism of formation of cerebral ischemia tolerance is not completely understood yet. It is possible that heat shock protein 70 (HSP70) in mitochondria, brain-derived erythropoietin, cell signaling pathways, TNF- $\alpha$ , Bcl-2 or neurotransmitters may be involved in formation of cerebral ischemia tolerance [10, 18-21]. The continuous development of molecular biology and genetic techniques makes it more possible to identify cerebral ischemia tolerance involving gene location and function. This then would provide new theoretical bases for new brain protective drug discovery, and open up new avenues to reveal new targets for ischemic cerebrovascular disease prevention and treatment. The inadequacy of this report is that the representation of patients may not be sufficient, since the sample size is small. Finally, long-term function and prognosis of patients with unilateral isolated basal ganglia lacunar infarction still need to be further confirmed.

In conclusions, there is a close relationship between the lesion location and other related factors such as lesions of cerebral white matter, history of cerebral infarction, history of diabetes and age, etc. and END in patients with isolated acute lacunar infarction in basal ganglia. Protective factors of END included age  $\geq 65$ , high systolic pressure, stroke history, cerebral white matter lesions in our study.

## Disclosure

The authors declare no conflict of interests for this paper.

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