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ORIGINAL ARTICLE

Influence of cerebral small vessel disease on functional outcome and recurrence of cerebral infarction in patients with type 2 diabetes

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Abstract

Objective To estimate the effect of the total cerebral small vessel disease score in the functional outcome and recurrence of cerebral infarction in patients with type 2 diabetes.

Methods A comparative study was used to review the initial cerebral infarction cases of patients with type 2 diabetes undergoing cranial MRI during 2016–2019, follow up their recovery for 3 months, and count the events of cerebral infarction recurrence within 24 months. MRI with lacunes, enlarged perivascular space (EPVS), cerebral microbleeds (CMBs), and white matter hyperintensities (WMHs) were defined as cerebral small vessel disease (CSVD). Chi-square tests, t-tests, rank-sum tests, and Logistic regression were used for the statistical analysis.

Results A total of 208 patients were included in the analyses. Mean age was 65.2 ± 11.8 years, and 62% were men. The distribution of the total SVD score from 0 to 4 was 26.9%, 23.6%, 26.4%, 16.3%, and 6.7%. Multivariate Logistic regression showed that the cumulative CSVD score was independently associated with poor outcome 3 months after cerebral infarction (OR:2.193, 95% CI:1.673–2.875) and recurrence within 2 years (OR:2.715, 95% CI: 1.363–2.979). Lacunes, CMBs, WMHs but not EPVS were associated with the modified Rankin Scale (mRS) scores at 3 months after cerebral infarction, Lacunes was associated with recurrence within 2 years. However, the impact of each CSVD marker on functional outcome and stroke recurrence was smaller than that of the total CSVD score.

Conclusion Cumulative CSVD burden exert important influences on the functional outcome and recurrence of cerebral infarction in patients with type 2 diabetes.

Keywords Cerebral microvascular disease · Type 2 diabetes · Stroke · Cerebral infarction

Introduction

With the rising number of adult patients with diabetes worldwide, type 2 diabetes has become a worldwide public health problem [1–3]. It is especially important to prevent the occurrence and recurrence of diabetic vascular complications, strokes, and ischemic heart disease. The risk of cerebral infarction in the diabetic population is more than twice as high as in the non-diabetic population, and long-term subclinical cerebrovascular injury exists prior to their cerebral infarction [4]. Numerous studies have shown that diabetes can lead to cerebral small vessel injury through various mechanisms such as abnormal polyol metabolism, hyper-glycolytic response, oxidative stress, abnormal transport of β-amyloid across the blood–brain barrier, and protein kinase C activation [5]. In clinical practice, experts currently define MRI manifesting lacunes of vascular origin, white matter hyperintensities (WMHs), enlarged perivascular

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space (EPVS), and cerebral microbleeds (CMBs) as CSVD [6]. Clinical studies have found that these image manifestations may be related to cerebrovascular events, but there is still a lack of systematic evidence [7]. In this study, various imaging manifestations of cerebrovascular disease in patients with type 2 diabetes were cumulatively scored, and their relationship with functional outcome and recurrence of ischemic cerebrovascular events was evaluated, so as to provide evidence for the prevention of diabetic cerebrovascular disease.

Materials and Methods

General data

The data of patients with primary cerebral infarction of type 2 diabetes who underwent head MRI examination in our hospital from January 2016 to December 2019 were reviewed. The modified Rankin Scale (mRS) score and ischemic stroke recurrence events within 2 years were recorded during follow-up. Clinical data such as gender, age, underlying diseases, cerebral infarction type and CSVD imaging markers were collected. This study was reviewed and approved by the hospital Ethics Committee.

Inclusion criteria and exclusion criteria

The 2 neurologists who were not involved in the case data collection read the MRI images respectively and then checked the unified opinion. The imaging markers of cerebrovascular disease were any one or more of lacunes of vascular origin, white matter hyperintensities, enlarged perivascular space, and cerebral microbleeds shown in MRI. CSVD cumulative score (0–4 scores): 0 score for normal, 1 score for each of the 4 MRI manifestations of lacunes of vascular origin, white matter hyperintensities, enlarged perivascular space > 10 mm, and cerebral microbleeds, and the scores were calculated cumulatively. Exclusion criteria: 1. History of stroke, 2. History of atrial fibrillation, 3. Severe hepatic and renal insufficiency, 4. Malignancy, 5. Death cases, 6. Poor MRI quality. The modified Rankin scale was used to measure the neurological recovery status of patients after stroke: 0 score for the patients who were completely asymptomatic; 1 score for the patients who can complete all daily work and life without obvious dysfunction despite symptoms; 2 score for the patients who were mildly disabled, unable to complete all activities before illness, but able to take care of their daily affairs without help; 3 score for the patients who were moderately disabled, requiring partial assistance but able to walk independently; 4 score for the patients who were moderately to severely disabled, unable to walk independently and requiring assistance in daily life; 5 score who were severely disabled, bedridden, incontinent and completely dependent on others in daily life. 0–2 score was classified as good neurological outcomes and 3–5 score as poor neurological outcomes.

Statistical analysis

SPSS 19.0 software was used for statistical analysis, and frequency, mean and median were used to represent categorical and continuous baseline variables. The one-way analysis of baseline variables was performed using Chi-square test, t-test or rank sum test. Variables with $p < 0.1$ in one-way analysis were included in logistic regression to determine the independent influencing factors of cerebral infarction recurrence or poor function. $p < 0.05$ was considered as a statistical difference.

Results

A total of 384 cases of type 2 diabetes cerebral infarction were reviewed, excluding 96 cases with a history of stroke, 12 cases of atrial fibrillation, 7 cases of severe hepatorenal insufficiency, 3 cases of malignant tumor, 3 cases of MRI quality inconsistent with the requirements. 263 cases were included in the follow-up, 19 cases died during hospitalization or within 3 months after discharge, 36 cases were lost to follow-up, and 208 cases were finally included in the statistical analysis. The flow chart of the case collection is shown in Fig. 1. The mean age was 65.2 ± 11.8 years old, of which 109 were males (52%) and 99 were females (48%). There were 109 cases with good functional outcome (mRS ≤ 2), and 22 cases with recurrent cerebral infarction within two years.

Univariate analysis showed that at 3 months after cerebral infarction, compared with the well-functioning group, the poorly functioning group was older, had higher NIHSS score at onset, had more MRI signs of white matter hyperintensities, lacunes, cerebral microbleeds, and had higher cumulative CSVD score ($p < 0.05$). In the univariate analysis of risk factors for recurrence, MRI manifestations of white matter hyperintensities, lacunes, cerebral microbleeds were statistically significant. The clinicopathological characteristics of the patients and the univariate analysis of functional outcome and recurrent cerebral infarction are shown in Table 1.

Variables with $p < 0.1$ in the univariate analysis were included in the logistic regression to determine the independent influencing factors of cerebral infarction recurrence or poor function. Multifactorial analysis showed that MRI with more white matter hyperintensities (OR = 1.84, 95%CI = 1.21–2.76, P = 0.004), lacunes (OR = 1.86, 95%CI = 1.25–2.74, $p < 0.001$), cerebral microbleeds (OR = 1.58,95%CI = 1.09–2.25, P = 0.002) signs, especially high cumulative CSVD scores (OR = 2.193,95%CI = 1.673–

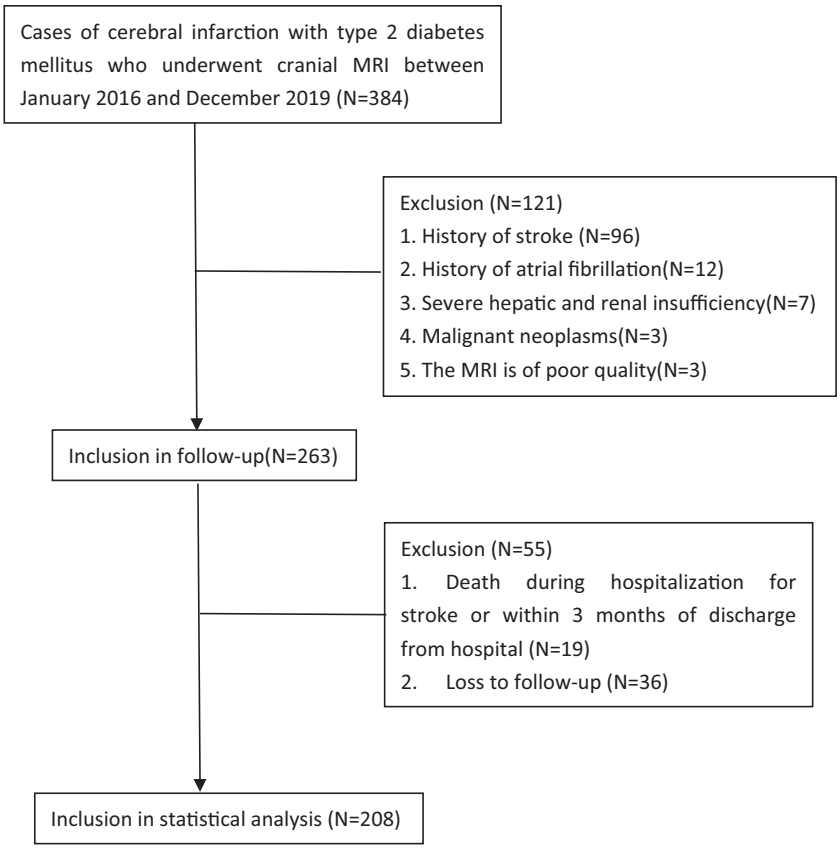

Fig.1 Flow chart of case collection

Table 1 Clinical characteristic of patients and univariate analysis of functional outcome and stroke recurrence

	The modified Rankin Scale (mRS)(3 months after cerebral infarction)			Recurrence (within 2 years)		
	≤2 (n = 109)	> 2 (n = 99)	*p*	No (n = 186)	Yes (n = 22)	P
Age (years)	60.5 ± 11.9	70.4 ± 9.3	< 0.001	64.9 ± 11.7	68.0 ± 12.9	0.243
Gender (Male)	68(62.4%)	61(61.7.3%)	0.909	116(62.3%)	13(59.1%)	0.765
Hypertension	77(70.6%)	80(80.8%)	0.089	144(77.4%)	13(59.1%)	0.069
Hyperlipemia	32(29.4%)	34(34.3%)	0.44	58(31.2%)	8(36.4%)	0.622
Smokers	53(48.6%)	46(46.5%)	0.755	86(46.2%)	13(59.1%)	0.254
Coronary heart disease	17(15.6%)	16(16.2%)	0.911	28(15.1%)	5(22.8%)	0.352
NIHSS	2.93 ± 0.988	5.47 ± 2.032	< 0.001	4.12 ± 2.011	4.27 ± 2.164	0.745
Cerebral infarction types			0.832			0.305
Large atherosclerotic type	50(45.9%)	43(43.4%)		85(45.7%)	8(36.4%)	
Small vessel occlusive type	23(21.1%)	26(26.3%)		45(24.2%)	4(18.2%)	
Cardiac embolism type	16(14.7%)	16(16.2%)		27(14.5%)	5(22.7%)	
Cerebral infarction with other definite causes	4(3.7%)	2(2.0%)		4(2.2%)	2(9.1%)	
Cerebral infarction with uncertain etiology	16(14.7%)	12(12.1%)		25(13.4%)	3(13.6%)	
white matter hyperintensities	19(17.4%)	79(79.8%)	< 0.001	82(44.1%)	16(72.7%)	0.011
lacunes	22(20.2%)	91(92.0%)	< 0.001	96(51.6%)	17(77.3%)	0.022
cerebral microbleeds	7(6.4%)	48(48.5%)	< 0.001	45(24.2%)	10(45.5%)	0.032
enlarged perivascular space	56(51.4%)	61(61.6%)	0.137	107(57.5%)	10(45.5%)	0.28
CSVD cumulative score	1.3 ± 1.143	1.77 ± 1.292	0.006	1.77 ± 1.490	2.41 ± 1.260	0.056

2.875, P = 0.004) were all independently associated with poor functional outcome at 3 months after cerebral infarction. Within 2 years after infarction, MRI with more lumens and a higher cumulative CSVD score was independently associated with recurrence Table 2.

Discussion

Microangiopathy is a unique chronic complication of diabetes and is more susceptible to various factors than large vessels, so the damage appears earlier and is more widespread, which is the basis for the occurrence of various diabetic complications. Diabetic cerebral microanglopathy is the pathological basis of brain complications, and early detection and diagnosis are of great significance to delay the course of the disease, prolong life and improve life quality [8–11]. On cerebral MRI imaging, small vessel injury can be manifested as: lacunes of vascular origin, white matter hyperintensities, enlarged perivascular space, and cerebral microbleeds [6]. Numerous clinical studies have found that these image features that can reflect the injury of small cerebral vessels are all risk factors for vascular diseases [12–14]. However, these imaging features often do not exist independently, and any one imaging feature cannot comprehensively measure the degree of cerebral small vessel injury, so some scholars have performed a semi-quantitative cumulative scoring of these imaging features to assess the degree of cerebral small vessel injury, which becomes the overall burden of cerebral small vessel disease. Clinical studies on its relationship with stroke, cognitive impairment, aging, etc. have also been conducted [15]. There are not yet any studies to apply this semi-quantitative assessment of cerebral small vessel disease in patients with diabetic cerebral infarction.

Our study showed that white matter hyperintensities, lacunes, and cerebral microbleeds were independently associated with functional outcomes in patients, which is consistent with the results of the current other studies. A study involving 5035 patients showed that patients with higher white matter hyperintensities signal load had worse mRS Scores at 3 months [16]. A recent meta-analysis showed that white matter hyperintensities, lacunes, cerebral microbleeds, and cerebral atrophy were associated with poor functional outcomes [17]. Our study did not find an association between enlarged perivascular space and functional outcome. More studies are needed to verify the relationship between enlarged perivascular space and functional outcome. Because imaging manifestations of cerebral small vessel disease often appear simultaneously in the same patient, and a single marker cannot fully reflect brain damage, scholars have proposed the concept of the overall burden of cerebral small vessel disease, and the method of CSVD cumulative score may be more beneficial to evaluate its clinical impact on patients. Our study found that the cumulative CSVD score was strongly associated with functional outcome in both univariate and multifactorial analyses, which is consistent with the current findings.

Patients with small cerebral vascular disease have a higher likelihood of recurrent cerebral infarction. Our study found that white matter hyperintensities, lacunes, and cerebral microbleeds were statistically significant in recurrent cerebral infarction in univariate analysis, while lacunes and CSVD accumulative scores were statistically significant in multivariate analysis. This may be caused by the error caused by the small sample size of our study. We speculated that patients with cerebral small vessel disease are more likely to have a recurrent stroke, and the higher the cumulative CSVD score, the more significant the predictive effect, which is consistent with the current research results. Xu et al. found that white matter hyperintensities, cerebral microbleeds and CSVD score are associated with recurrent stroke [13]. Cheng et al. found that factors associated with increased risk of recurrent stroke were white matter high signal, lacunae and CSVD score [17]. CSVD reflects severe brain damage that reduces the efficiency of neural connections and workings, leading to a slower recovery of patients after stroke, which is a possible mechanism that leads to an increased risk of recurrent stroke. Both Tian and Umeno's studies verified the role of CSVD score in predicting stroke recurrence [18, 19].

Table 2 Multivariate analysis of functional outcome and stroke recurrence

	The modified Rankin Scale (mRS) (3 months after cerebral infarction)			Recurrence (within 2 years)		
	OR	95% CI	*p*	OR	95% CI	*p*
White matter hyperintensities	1.84	1.21–2.76	0.004	2.14	0.83–5.34	0.203
Lacunes	1.86	1.25–2.74	< 0.001	2.07	1.19–4.86	0.020
Cerebral microbleeds	1.58	1.09–2.25	0.002	2.16	0.92–5.03	0.086
Enlarged perivascular space	1.07	0.75–1.68	0.47	1.06	0.47–2.83	0.87
CSVD cumulative score	2.193	1.673–2.875	0.004	2.715	1.363–2.979	0.023

Conclusion

Our study found that specific imaging markers of cerebral small vessel disease and cumulative CSVD scores in diabetic infarct patients could be used as predictors of functional outcome after infarction and were associated with recurrence of infarction in the short term. This study still has the following limitations: 1. Patients with severe stroke who underwent vascular recanalization therapy were not included in this study, because CSVD is associated with functional outcome in patients receiving thrombolysis and intravenous thrombolysis, and selection bias may affect the impact of cumulative CSVD score on functional outcome. 2. The data are from a single center, and the generalizability of the findings has certain limitations.

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Declarations

Ethics approval and consent to participate Ethical approvals were obtained from the Institutional Ethics Committees of Department of Neurosurgery, People's Hospital of Haimen District, Nantong City, Jiangsu Province, China. All the study participants provided written informedconsent.

Competing interests The authors declare no competing interests.

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