Stroke Type, Etiology, Clinical Features and Prognosis of Diabetic Patients in Southern China

Ting Yang, PhD[1], Kai Fan, PhD[2], Yungang Cao, PhD[3] ⓘ,
Jueyue Yan, PhD[3], and Zhao Han, PhD[3] ⓘ

Abstract

To analyze the type, etiology, clinical features and prognosis of stroke in southern China diabetic patients. From January to August 2019, acute stroke patients were prospectively enrolled in the Wenzhou Stroke Registry within 7 days of admission to the Hospital. The differences between the 2 groups of stroke patients with or without diabetes were in the following aspects: bleeding site of hemorrhagic stroke, different ischemic stroke etiology, Oxfordshire Community Stroke Project (OCSP) classification, death and disability within 3 months. Of the 497 patients enrolled, 104 (20.9%) were diabetic patients. 114(22.9%) patients had hemorrhagic stroke. The incidence of hemorrhagic stroke in the diabetic group was 10.6%, deep hemorrhage stroke account for 90.9%.In patients with ischemic stroke, the proportions of the new Trial of Org 10172 in Acute Stroke Treatment (TOAST) etiological subtype classifications (atherothrombosis (AT), cardioembolism (CE), small artery disease (SAD), stroke of other determined etiology (SOD) and stroke of undetermined etiology (SUD)) in the diabetic (non-diabetic) group was 43% (31%), 7.5% (14.1%), 27.9% (16.9%), 1% (0.3%), and 20.4% (37.6%), respectively; the proportion of The OCSP classifications(total anterior circulation infarcts(TACI), partial anterior circulation infarcts(PACI), lacunar infarcts(LACI) and posterior circulation infarcts(POCI)) in the diabetic (non-diabetic) group was16.1% (22%), 30.1%(37.2%), 42% (31.4%), and 10.8% (9%), respectively. The 3-month poor prognosis of the diabetic and non-diabetic groups was 23.1% and 28.2%. For diabetic patients, the incidence of hemorrhagic stroke is low, deep hemorrhage is common; SAD and LACI are common in the ischemic stroke; There was no significant difference in the 3-month prognosis between the 2 groups.

Keywords

stroke, diabetes complications, clinical features, prognosis

Introduction

Stroke is a leading cause of mortality and disability in the worldwide.[1] In our country, stroke is the leading cause of death and causes a very serious burden of disease.[2] According to the Global Burden of Disease (GBD) 2016 study, potentially modifiable risk factors cause much of the stroke burden,[1] and more than 75% of this burden could be reduced by controlling metabolic and behavioral risk factors.[3] Diabetes mellitus is an important potentially modifiable risk factor for stroke. Diabetic patients suffer stroke of all types and are at ongoing risk for both acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH). The risk of stroke is 2-4 times higher among patients with diabetes than among matched healthy controls.[4]

To our knowledge, domestic literature on the type, clinical characteristics and prognosis of stroke in diabetic patients is rare, the sample sizes are small, and the quality is not high; therefore, it is necessary to study the characteristics of stroke in

[1] Department of Emergency, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province, China
[2] Department of Neurology, Zhoukou Central Hospital, Henan Province, China
[3] Department of Neurology, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province, China

Corresponding Author:
Zhao Han, Department of Neurology, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province, China.
Email: wzhanzhao@aliyun.com

diabetic patients. Based on the establishment of the Wenzhou Stroke Registry, this study prospectively registered patients who had been diagnosed with stroke within 7 days from onset to admission. The demographic characteristics, risk factors, subtypes of stroke, clinical characteristics and prognosis of patients with and without diabetic stroke were compared to understand the characteristics of diabetic stroke in Chinese patients. Improving the understanding of diabetic stroke and providing a theoretical basis for individual clinical decision-making will be of great practical and clinical significance in improving the prognosis of stroke and reducing death from and recurrence of stroke.

Materials and Methods

Methods

A prospective cohort study was conducted to investigate the relationship between the type, etiology and prognosis of stroke in diabetic and non-diabetic patients.

Research subjects: From January 2019 to August 2019, the Department of Neurology and Emergency Department of the First Affiliated Hospital and the Second Affiliated Hospital of Wenzhou Medical University continuously admitted patients with a first diagnosis of acute stroke; all patients with stroke symptoms, except those patients with subarachnoid hemorrhage, should have undergone urgent neuroimaging by either non-contrast computed tomography(CT) or magnetic resonance imaging (MRI).[5] The inclusion criteria were as follows:(1) the diagnosis met the criteria for an acute stroke(ischemic stroke and intracerebral hemorrhage)[6]; (2) the symptom onset to admission time was less than or equal to 7 days; (3) a 3-month follow-up assessment was completed; and (4) patients or their families signed the informed consent form. The exclusion criteria were as follows:(1) patients with an unclear onset time; (2) patients with other diseases that affected physical movement, the coordination and balance function or speech function, and daily self-care abilities; (3) patients diagnosed with a transient ischemic attack, a stroke mimic or a final diagnosis of other diseases;(4)patients with a simple subarachnoid hemorrhage.

Research Methods

Neurologists were trained to complete a standardized registration form for theWenzhou Stroke Registry Program (WSRP), which includes basic data, within 24 hours of admission; the data include the patient's clinical characteristics, the Oxford-shire Community Stroke Project(OCSP)[7] classification(total anterior circulation infarcts(TACI), partial anterior circulation infarcts(PACI), posterior circulation infarcts(POCI), and lacunar infarcts(LACI)), demographic data(name, sex, age), family medical history, previous medical history(diabetes mellitus, hypertension, heart disease, hyperlipidemia, history of stroke, smoking and alcohol abuse, etc.), degree of neurological impairment at admission (using the National Institutes of Health Stroke Scale (NIHSS) score), first fasting blood tests

after admission (blood sugar, total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL)), the results of auxiliary examinations during hospitalization (including echocardiography, transcranial Doppler (TCD) ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA)), the lesion location (cortex, basal ganglia, brain stem, cerebellum), main complications (urinary tract infection, pulmonary infection, upper gastrointestinal bleeding, etc.) and the discharge etiological classification of ischemic strokefrom the new Trial of Org 10172 in Acute Stroke Treatment (TOAST) etiological classification, which includes 5 subtypes of brain infarction: atherothrombosis (AT), cardioembolism (CE), small artery disease (SAD), stroke of other determined etiology (SOD) and stroke of undetermined etiology (SUD)).[8]

The outcomes at 3 months after stroke onset were assessed with the modified Rankin Scale (mRS).[9] A favorable outcome was defined as an mRS score of 0-2, and an unfavorable outcome was defined as an mRS score of 2-6.

Statistical Methods

Statistical analyses were performed using SPSS version 20. Data are presented as the means $\pm$ standard deviations for continuous variables and as counts and percentages (%) of subjects for categorical variables. Univariate comparisons of 2 groups were performed with Student's t-test or the Mann-Whitney U test for continuous variables and Pearson's χ^2 test for categorical variables. Logistic regression was used to analyze the multiple factors affecting 3-month mortality/disability in the diabetic and non-diabetic groups. The results were considered statistically significant when $P < 0.05$.

Results

1. General data: In total, 497 acute stroke patients were included in our study: 305 men (61.4%) and 192 women (39.6%). Among them, 104 (20.9%) had diabetes mellitus, 375 (75.5%) had hypertension, 40 (8.0%) had hyperlipidemia, 27 (5.4%) had coronary heart disease, 44 (8.9%) had atrial fibrillation, 60 (12.1%) had a history of stroke and 126 (25.4%) were smokers.

Demographic Characteristics and Risk Factors for Diabetes Mellitus

The comparison between the 2 groups showed that the sex distribution was obviously different, and that the incidence of stroke in women in the diabetic group was significantly higher than in women in the non-diabetic group (49% vs 36%, respectively, P = 0.014). The mean age of stroke onset was approximately 2.5 years older in the diabetic group than in the non-diabetic group(66.63 + 10.59 vs 64.10 + 13.12, respectively, P = 0.041).There was no significant difference in the traditional risk factors for stroke between the diabetic group and the non-diabetic group, which include hypertension,

Table 1. General Characteristics and Univariate Analysis of Diabetic and Non-Diabetic Stroke Patients.

Variable	Diabetic Group N = 104	Non-diabeticGroup N = 393	T or χ^2value	P value
Female, n (%)	51 (49%)	141 (36%)	6.008	0.014*
Female, n (%)	51 (49%)	141 (36%)	6.008	0.014*
Age (median)	66.63 $\pm$ 10.59	64.10 $\pm$ 13.12	-2.05	0.041*
Hypertension, n (%)	84(80.7%)	291(74.0%)	2.007	0.157
CHD, n (%)	7(6.73%)	20(5.09%)	0.395	0.530
Atrial fibrillation, n (%)	5(4.8%)	39(9.9%)	2.761	0.097
Hypercholesterolemia,n (%)	11(10.6%)	29(7.4%)	1.136	0.286
Previous stroke, n (%)	17(16.3%)	43(10.9%)	2.263	0.132
Previous TIA, n (%)	2(1.9%)	5(1.3%)	0.001	0.974
Current smoker, n (%)	21(20.2%)	105(26.7%)	1.850	0.174
Alcohol drinking, n (%)	15(14.4%)	86(21.9%)	2.826	0.093
Admission TG level	2.081 $\pm$ 1.414	1.515 $\pm$ 0.905	-3.875	0.000*
Admission TC level	4.798 $\pm$ 1.179	4.487 $\pm$ 0.980	-2.438	0.016*
Admission HDLlevel	1.024 $\pm$ 0.330	1.096 $\pm$ 0.294	2.161	0.31
Admission LDL level	3.132 $\pm$ 0.868	2.900 $\pm$ 0.847	-2.469	0.014*
Admission NIHSS score	6.56 $\pm$ 5.720	7.39 $\pm$ 7.067	-1.114	0.266
Admission GCS score	14.41 $\pm$ 1.753	14.02 $\pm$ 2.402	-1.821	0.070
Aspirin n (%)	41(39.4%)	186(47.3%)	2.071	0.15
Clopidogrel, n (%)	30(28.8%)	15(3.8%)	62.565	0.000*
Warfarin,n (%)	2(1.9%)	16(4.1%)	Fisher	0.388
NOAC,n (%)	1(0.96%)	6(1.5%)	Fisher	1.000
Statin,n (%)	46(44.2%)	117(29.7%)	7.801	0.005*

CHD = coronary heart disease; * = Statistical significance.; NOAC = non vitamin K antagonist oral anticoagulants, NOAC.

Table 2. Comparison of the Cerebral Hemorrhage Sites Between Diabetic and Non-Diabetic Groups.

Stroke type	Diabeticgroup N = 104	Non-diabetic group N = 393	Total N = 497	χ^2value	P value
Hemorrhagic	11(10.6%)	103(26.2%)	114	11.368	0.001
Deep hemorrhage	10(90.9%)	77 (74.8%)	87	0.680♦	0.410♦
Lobar	1 (9.1%)	26 (25.2%)	27	0.680♦	0.410♦
ischemic	93 (89.4%)	290(73.8%)	383	11.368	0.001

♦Represents the continuity-corrected χ^2 value and p value.

coronary heart disease, atrial fibrillation, hyperlipidemia, and a history of stroke, TIA, smoking and alcohol consumption. However, the blood lipid disorders after admission showed statistically significant differences between the 2 groups: TG, TC, and LDLwere significantly higher in the diabetic group than in the non-diabetic group. The treatment rate of clopidogrel and statin in the diabetes group before admission was significantly higher than that in the non-diabetic group, while the treatment rate of aspirin, warfarin and NOAC was not different (Table 1).

Types of Stroke

Intracerebral Hemorrhage

The incidence of cerebral hemorrhage in the diabetic group was 10.6% (11/104), which was statistically significantly lower than that in the non-diabetic group (26.2%,103/393). The hemorrhage sites were different between the 2 groups, and deep hemorrhage was more common in the diabetic group than in the non-diabetic group (90.9% vs 74.8%, respectively), while lobular hemorrhage was more common in the non-diabetic group than in the diabetic group (25.2% vs 9.1%, respectively) (Table 2).

Comparison of Different Types of Cerebral Infarction

The incidence of cerebral infarction in the diabetic group (89.4%,93/104) was statistically significantly higher than in the non-diabetic group (73.8%,290/393). According to the new TOAST etiological classification method, AT and SAD were more common in the diabetic group than in the non-diabetic group, with 43% vs 31% ($\chi^2 = 4.505$, P = 0.034) and 27.9% vs 16.9% ($\chi^2 = 5.470$, P = 0.019), respectively. There was a significant difference between the 2 groups. Following the OCSP classification of clinical manifestations, lacunar infarctin the diabetic group was more common than in the non-diabetic group (42% vs 31.4%;$\chi2 = 3.972$, P = 0.046),

Table 3. Comparison of Clinical Characteristics Between the Diabetic and Non-Diabetic Groups.

	Diabeticgroup N = 104	Non-diabetic group N = 393	T or χ^2value	P value
NIHSS score	6.56 $\pm$ 5.720	7.39 $\pm$ 7.067	-1.114	0.266
Complications	14(13.5%)	61(15.5%)	0.272	0.620

Table 4. Follow-up and Prognosis of Patients at 3 Months After Onset.

	Diabeticgroup N = 104	Non-diabetic group N = 393	χ^2	P
Lost to follow-up	3 (2.9%)	17(4.6%)	0.148	0.701
Death	5(4.8%)	10 (2.5)	0.723	0.395
MRS 0-2	77(74%)	270(68.7%)	0.788	0.375
MRS 3-5	19(18.3%)	96(24.4%)	1.965	0.161
Poor prognosis (Death + MRS 3-5)	24(23.1%)	106(27%)	0.788	0.375

Table 5. Multivariate Logistic Regression of Death and Disability 3 Months After Stroke.

Variable	B	BE	Wald	P	Exp(B)	95.0% CI
NIHSS score	-0.134	0.019	51.880	0.000*	0.874	0.843-0.907
Diabetes	0.016	0.281	0.003	0.956	1.106	0.581-1.777
Atrial fibrillation	-0.754	0.378	3.974	0.046*	0.470	0.224-0.987
Hypertension	0.417	0.254	2.708	0.100	1.518	0.923-2.495
Hyperlipidemia	0.101	0.402	0.063	0.802	1.106	0.503-2.430
CHD	-0.312	0.470	0.440	0.507	0.732	0.291-1.840
History of stroke	-0.220	0.350	0.397	0.529	0.802	0.404-1.592
Current smoker	-0.355	0.255	1.932	0.165	0.701	0.425-1.157

CHD = coronary heart disease; * = Statistical significance.

and there was a significant difference between the 2 groups. The next most common OCSP subtype was posterior circulation infarct in 10.8% vs 9% of patients, respectively, but there was no significant difference between the 2 groups.

The clinical features of stroke. There was no significant difference in the severity of illness (NIHSS score) and the incidence of complications between the 2 groups (see Table 3).

Prognostic and Predictive Factors of Stroke

At the end of the 3-month follow-up period, 20 cases (4%) were lost to follow-up.Among the101 patients with diabetes mellitus, 24 had a poor prognosis (23.1%), and among the 376 patients without diabetes, 106 had a poor prognosis (28.2%);there was no significant difference between the 2 groups ($\chi2$ = 0.788 P = 0.375) (see Table 4).Multivariate logistic regression analysis showed that a poor prognosis at the 3-month follow-up was associated with severe neurological

deficits and a history of atrial fibrillation at admission but not with diabetes mellitus and hypertension (see Table 5).

Discussion

Our prospective study enrolled 497 consecutive patients with acute stroke, including 104 diabetic patients and 393 non-diabetic patients.We found that stroke in diabetic patients has the following characteristics: (1) The incidence rate for women is high, and the mean age of onset was older; (2) The average levels of TG, TC and LDL in diabetic patients were higher than those in non-diabetic patients. (3) Non-diabetic patients with cerebral hemorrhage have a low incidence of cerebral infarction, and diabetic patients with cerebral hemorrhage have a high incidence of cerebral infarction. (4) Regarding the location of the cerebral hemorrhage, deep hemorrhage was more common in diabetic patients, and lobar hemorrhage was more common in non-diabetic patients. (5) In the etiological classification of the ischemic stroke subtype, SAD and AT were the most common types in the diabetic group. (6) In the OCSP classification of the ischemic stroke subtype, LACI are the most common type in the diabetic group. (7) The NIHSS score, complications and prognosis at 3 months were not different between the 2 groups.

The incidence of diabetes mellitus in stroke patients was 20.9%, which was similar to other studies.[10-12] Our study found that the incidence of stroke in diabetic women was significantly higher than that in non-diabetic women. This conclusion supports previous studies.[11] The Diabetes and Genetic Epidemiology Unit, Department of Epidemiology and Health Promotion, National Public Health Institute of Finland epidemiological investigation shows that, when suffering from diabetes, the risk of women suffering from cardiovascular and cerebrovascular disease is higher than that of men.[13] Another prospective cohort study found that the risks of ischemic stroke or transient ischemic attack for women with metabolic syndrome are 1.5 times those for men.[14] We found that stroke patients in the

diabetic group were 2.5 years older than patients in the non-diabetic group. Our study was consistent with the results of the Lausanne Stroke Registry in Switzerland,[15] a study of 4,064 consecutive patients(611 diabetic individuals) showed that the age of stroke onset in diabetic patients was 5.3 years older than that in non-diabetic patients. However, the Copenhagen Stroke Study has reported that the onset age of stroke in the patients with diabetes is earlier than that in patients without diabetes.[16] Therefore, the age difference for stroke in diabetic patients needs to be further studied or followed up in the population.

We found that the admission blood lipid index of the diabetic group was significantly higher than that of the non-diabetic group, with statistical significance. However, there were few people with 'history of hyperlipidemia, and there was no difference between the 2 groups. The reasons may be as follows: (1) Diabetes mellitus itself is characterized by abnormal blood lipid metabolism, and the proportion of patients with hyperlipidemia is high; (2) People's recognition rate of abnormal blood lipid levels is low, which is related to people's lack of attention to routine physical examinations of blood sugar, blood lipids and other indicators and the lack of primary prevention knowledge.

We found that the incidence of cerebral hemorrhage was lower in the diabetic group, which was consistent with the results of the Lausanne Stroke Registry in Switzerland.[15] The Lausanne Stroke Registry found that cerebral hemorrhage was rare in stroke patients with diabetes mellitus and that there was no interaction between diabetes mellitus and hypertension. However, this conclusion needs to be confirmed by future population-based data. Because these studies are cross-sectional analyses, exposures and outcomes occur at the same time, and we cannot conclude that diabetic angiopathy has a protective effect on cerebral hemorrhage. However, we can speculate that diabetes-induced basement membrane thickening and endothelial hyperplasia reduce the probability of cerebral vascular rupture. In addition, the levels of platelet aggregation, coagulation and plasminogen activator inhibitors are increased in diabetic patients, while the activity of fibrinolysis was decreased, which also reduced the incidence of cerebral hemorrhage. The proportion of deep hemorrhage sites was higher in the diabetic group than in the non-diabetic group (90.9% vs 74.8%, respectively). Although there was no significant difference between the 2 groups, we think it has certain clinical significance. The proportion of diabetic patients with hypertension is high:80.7% of patients in the diabetic group have hypertension and 70.4% of patients in the non-diabetic group have hypertension. Hypertension is a very important cause of deep cerebral hemorrhage.

The subtypes of ischemic stroke were different between the diabetic and non-diabetic groups.We found that SAD and AT are common in diabetic patients, which is similar to the findings the international and Chinese literature.[15,17] The cause may be related to cerebrovascular disease caused by diabetes mellitus. Because of metabolic disorders related to sugar, fat and protein, diabetic patients not only have cerebral macrovascular lesions but also can have rapidly developing cerebral

microvascular lesions, resulting in distal small vessel dystrophy, wall degeneration, necrosis and dysfunction of the fibrinolytic system, which eventually lead to atherosclerotic lesions of the great arteries and lacunar lesions of the small arteries. We also found that a higher proportion of diabetic patients than non-diabetic patients had a posterior circulation infarct, suggesting that diabetic patients were more susceptible to posterior circulation infarction.

This study found that there was no difference in stroke severity and 3-month prognosis between the diabetic and non-diabetic groups at admission. The logistic regression model showed that poor 3-month prognosis was not associated with diabetes but with severe neurological deficits and atrial fibrillation at admission. In a hospital-based study, Kiers L. et al. found that diabetic stroke was more severe, but the number of diabetic patients included in this study was very small, and further observation was needed.[16] Nannetti et al. showed that diabetes had no effect on motor and functional prognosis in acute and post-acute stages of stroke.[18] A multi-center study in the European Union found that the disability and dysfunction of diabetic patients increased significantly in 3 months, but the mortality rate was not high.[19] Previous studies by Jorgensen et al. reported that the mortality rate of diabetic patients was higher than that of non-diabetic patients, and the functional prognosis of survivors was similar, but their recovery might be slower,[17] however, Szczepanska-Szerej et al. reported that diabetes has no effect on the course and outcomes of ischemic stroke.[20] Reeves et al. found that the in-hospital mortality rate of diabetic patients was higher than that of non-diabetic patients.[21] These contradictory conclusions can be explained by the number of patients, the use of the functional prognosis scale and the different follow-up times. Therefore, the impact of diabetes on the prognosis of stroke patients still needs to be confirmed by large-sample population-based studies.

This study has the following limitations: (1) This study reflects only the situation of inpatients in 2 tertiary hospitals, not the overall situation of stroke patients in China, and further community-based research needs to be performed under certain conditions, or multi-center large-sample research to reduce bias and draw more reliable conclusions; (2) Due to the limitations of the conditions, this study on diabetes mellitus patients did not include a stratified analysis of blood sugar levels in diabetic patients, and further research is needed to explore the relationship between blood sugar levels and the prognosis of diabetic patients.

Conclusion

The clinical characteristics and prognosis of 104 diabetic patients and 393 non-diabetic patients in the Wenzhou Stroke Database were compared. The preliminary conclusions are as follows: (1) The onset age of stroke in diabetic patients was late, and most of the diabetic patients were women and had abnormal blood lipids. (2) Diabetic patients are prone to ischemic stroke. The incidence of hemorrhagic stroke is low, and deep hemorrhages are common. (3) AT and SAD are the

most common etiological types of ischemic stroke in patients with diabetes mellitus. (4) Lacunar infarction and posterior circulation infarction are common in diabetic patients with ischemic stroke syndrome. (5) There was no correlation between diabetes mellitus and neurological impairment at admission and disability/death at 3 months post-admission

Author Contribution

TingYang and KaiFan contribute equally to this work.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from all patients or their legal guardian.

ORCID iD

Yungang Cao 🔟 https://orcid.org/0000-0003-3378-8132
Zhao Han 🔟 https://orcid.org/0000-0002-0901-9870

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