Stroke Occurring on the Left or Right Side of the Brain Can Be Identified by the Analysis of Retinal Images: A Case Control Study

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Abstract

Background: The burden of stroke in China has increased dramatically in the past 30 years. Specifying the treatment according to the side of stroke in the brain might be an effective way to reduce the burden. Current imaging tools to identify the side of brain stroke, such as magnetic resonance imaging (MRI), are expensive and time-consuming. Hence, there is a great need for a rapid and inexpensive assessment. In this case, retinal image analysis is a possible approach for stroke side identification. This study aimed at determining the association between retinal characteristics and the stroke side and to establish a predictive model for further investigation.

Methods: A total of 168 patients (89 left-sided stroke patients and 79 right-sided stroke patients) were recruited from the Shenzhen Traditional Chinese Medicine Hospital in the study. Retinal characteristics were analysed using an automated retinal image analysis (ARIA) system. Multivariable logistic regression was used to identify and develop predictive models.

Results: Each unit increase in the right eye bifurcation coefficient of arterioles increased the risk of right-side stroke by 7.523 times (95% CI, 1.823–31.044). Additionally, an elevated bifurcation coefficient of venules in the right eye also increased the risk of stroke in the right side of the brain, with an odds ratio (OR) of 7.377 (95% CI, 1.771–30.724). A complex retinal composite score was also associated with a higher risk of right-side stroke (OR, 4.955; 95% CI, 3.061–8.022).

Conclusions: This study demonstrated that retinal images can provide useful information for stroke side identification, and specific retinal characteristics may help predict the occurrence of stroke.

Trial registration: Acupuncture Clinical Trail Redistry, ChiCTR1800019647, Registered 01 November 2018, AMCTR-OPC-18000228.

Introduction

Stroke has become the leading cause of death in China with an increased disease burden for the last 30 years. The rapidly ageing population is one of the major reasons for this high prevalence.(1, 2) The location of stroke in the brain has a strong influence on the clinical consequences.(3) In most cases, stroke occurs only in one hemisphere of the brain and results in impairment on the opposite side of the body. Studies reveal that stroke in the left hemisphere affects motor control(4) as well as language and speech,(5) whereas right hemisphere stroke affects spatial orientation and posture.(4) Therefore, specific clinical advice and treatments are required for the patients depending on the stroke side.

Current techniques for stroke diagnosis have been well studied and accepted. Neurological examinations, such as the National Institutes of Health Stroke Scale (NIHSS) and Barthel index, provide information on the severity of stroke and activities of daily living, whereas imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) scans assist in stroke diagnosis by identifying the locations and damages in the brain.(6) However, these techniques have some limitations, CT imaging exposes the patients to a high radiation dose while MRI is an expensive, time-consuming, and environment-restricted procedure.(6, 7) Therefore, there is a great need for new tools that can rapidly differentiate the damaged side of the brain after strokes at a relatively low cost.

The function of the retina makes it one of the most metabolically active tissues in the body and the double vascular network maintains its blood supply. A small part of the circulation can be observed directly through the retina.(8) Previous studies have shown that some characteristics of retinal microvasculature are associated with strokes, which may be predicted by computational retinal analysis.(9–14) Most studies have investigated only the risks or other aspects of strokes but the association between retinal parameters and the stroke side has not been demonstrated so far. In this study, retinal parameters were extracted from colour fundus retinal images and the retinal characteristics were used via a logistic model to explore the association further.

Methods

Data source

In this study, 254 stroke patients from Shenzhen Traditional Chinese Medicine Hospital were enrolled. Baseline data, including age, sex, medical history, physical examination, laboratory tests, NIHSS, and Barthel index were collected. All patients underwent a detailed cranial MRI scan.

All patients were diagnosed with either left or right hemispheric stroke, aged 30–80 years, with an adequate sitting balance to undergo retinal photography. Patients aged over 80 years were not included in the study because of much higher prevalence of age-related optical opacity and other comorbidities as compared to the younger patients, making them unsuitable for retinal photography and may have caused a bias. Patients with eye diseases influencing the retinal vasculature, and those who are physically or subjectively unable to comply with MRI scans were excluded. Furthermore, subjects suspected to have cerebral diseases and those with diseases influencing vessel morphology were also excluded. Ultimately, 168 of the 254 patients who presented with stroke were included in this study.

The clinical and radiological information of the patients along with the stroke side was evaluated and their association with retinal characteristics were analysed.

Retinal characteristics

Retinal characteristics include retinal vessel measurements, arteriole-venous nicking, arteriole occlusion, tortuosity, haemorrhage, exudates, asymmetry of branches, bifurcation coefficients (BC), and bifurcation angles (BA). According to the formula developed by Knudtson *et al.*, the retinal vessel measurements were summarized into central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE), representing the diameters of arterioles and venules respectively.(15) The arteriole-to-venule ratio (AVR) was calculated as the ratio of CRAE to CRVE. Vessel tortuosity provides both qualitative and quantitative information by visual grading of one fovea-centred and one disc-centred fundus image. Arteriole venous nicking results in narrowing of the venule when crossed by an arteriole, and arteriole occlusions referred to the blockage of blood flow inside the arterioles when obstructed by an emboli. The branching pattern of retinal vessels, such as bifurcation coefficient (BC); the ratio of the widths of branching vessels to trunk vessels, bifurcation angle (BA); the angle between two branching vessels and asymmetry; the ratio of diameters of two branching vessels demonstrate the relationship between the trunk and the branching vessels. The fractal dimension (FD) of the retinal vasculature measured the complexity of branching patterns. The analysis was performed using three sets of vessels in one retinal image. Haemorrhages and exudates were recorded as present or absent and indicated in probability (0 to 1).

Statistical Analysis

Descriptive statistics, chi-square tests, and two-tailed independent samples t-tests were used to compare the demographics and retinal characteristics between the left and right stroke sides. A p-value < 0.05 was considered statistically significant. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were obtained by logistic regression to control for confounding. Stepwise multivariable logistic regression was employed to select the best model. The classification accuracy and the area under the receiver operating characteristic (ROC) curve were measured. Leave-one-out classification was used to validate the developed model. All the data was analysed using SPSS 25.0 software (IBM, New York, USA).

The fully automatic retinal image analysis method was developed using R (University of Auckland, Auckland) and MATLAB (MathWorks, Massachusetts, USA) computer software. The detailed procedure of the automatic retinal imaging analysis can be found in Zee.(16)

Results

Descriptive demographic variables

In total, 168 patients (133 men and 35 women) with mean age of 55.72 years, 89 left-side strokes and 79 right-side strokes were analysed in this study. Among these patients, 113 (67.3%) had ischemic strokes and 50 (29.8%) had haemorrhagic strokes. Smokers and drinkers in this analysis include both current and former status. A summary of the demographic variables is listed in Table 1. In general, there was no significant difference in demographics between the patients with stroke on the left side and the right side.

Table 1
Demographic data of patients with stroke in the left and right sides.

	Total (n = 168)	Left side (n = 89)	Right Side (n = 79)	p-Value
Male (n/%)	133 (79.2%)	70 (78.7%)	63 (79.7%)	.862
Age (mean ± SD)	55.72 ± 10.89	56.61 ± 10.61	54.72 ± 11.18	.264
BMI (mean ± SD)	23.29 ± 2.80	23.27 ± 2.69	23.31 ± 2.94	.930
Smoker (%)	50 (29.7%)	26 (29.2%)	24 (30.4%)	.531
Drinker (%)	31 (18.5%)	15 (16.8%)	16 (20.2%)	.845
Insomnia (%)	56 (33.3%)	28 (32.2%)	28 (35.4%)	.926
Hypertension (%)	135 (80.4%)	73 (83.9%)	62 (78.5%)	.370
Diabetes (%)	55 (32.7%)	27 (30.3%)	28 (35.4%)	.481
Stroke Type				
Ischemic (%)	113 (67.3%)	57 (64.0%)	56 (70.9%)	.139
Haemorrhagic (%)	50 (29.8%)	31 (34.8%)	19 (24.1%)	
Both (%)	5 (3.0%)	1 (1.1%)	4 (5.1%)	

*p-Value < 0.05.

Univariate analysis of retinal characteristics

Table 2 summarizes the retinal characteristics of the left and right eyes of the patients. From the results of univariate analysis, only venous asymmetry (Vasymmetry) in the left eye showed a slight but significant decrease in left-side stroke with an odds ratio (OR) of 1.227 (95% CI, 1.053–1.431; P = 0.009). However, for other retinal characteristics, there was no significant difference between left-side and right-side strokes in either the left or right eye.

Table 2
Retinal characteristics of left and right eyes among patients with stroke in the left and right sides.

	Left Eye (Mean ± SD)			**Right Eye (Mean ± SD)**		
	Left side (n = 89)	Right side (n = 79)	p-Value	Left side (n = 89)	Right side (n = 79)	p-Value
CRAE	14.41 ± 1.68	14.61 ± 0.78	.371	13.96 ± 0.58	14.00 ± 0.67	.653
CRVE	20.86 ± 2.32	21.12 ± 0.77	.406	20.78 ± 0.68	20.84 ± 0.76	.580
AVR	0.69 ± 0.04	0.69 ± 0.02	.581	0.67 ± 0.02	0.67 ± 0.02	.992
BCV	2.04 ± 7. 21	1.29 ± 0.02	.660	1.34 ± 0.13	1.33 ± 0.12	.613
BCA	1.61 ± 0.16	1.64 ± 0.07	.169	1.44 ± 0.47	1.51 ± 0.41	.353
Venous Angle	67.82 ± 7.62	68.53 ± 2.13	.470	69.03 ± 2.36	69.01 ± 2.29	.970
Artery Angle	70.31 ± 7.75	71.49 ± 1.49	.156	59.68 ± 25.45	62.57 ± 22.20	.436
Vasymmetry	0.76 ± 0.06	0.77 ± 0.02	.009*	0.78 ± 0.03	0.78 ± 0.02	.392
Aasymmetry	0.83 ± 0.06	0.83 ± 0.01	.491	11.46 ± 24.76	8.60 ± 21.83	.430
AVNicking	0.31 ± 0.07	0.31 ± 0.08	.932	0.27 ± 0.08	0.27 ± 0.09	.697
Tortuosity	0.39 ± 0.14	0.38 ± 0.06	.520	0.36 ± 0.06	0.37 ± 0.07	.298
Haemorrhage	0.22 ± 0.06	0.22 ± 0.06	.937	0.19 ± 0.07	0.20 ± 0.07	.174
Arteriole occlusion	0.09 ± 0.04	0.09 ± 0.03	.414	0.14 ± 0.13	0.12 ± 0.07	.174
FDa	1.16 ± 0.17	1.18 ± 0.01	.262	1.31 ± 1.22	1.18 ± 0.01	.845
FDv	1.18 ± 0.10	1.19 ± 0.01	.632	2.52 ± 11.33	1.32 ± 1.26	.544

*p-Value < 0.05.

Abbreviations:

CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; AVR, Arteriole-to-venule diameter ratio; BCV, bifurcation coefficient of venules; BCA, bifurcation coefficient of arterioles; FDa, fractal dimension of arteriolar network; FDv, fractal dimension of venular network.

Multivariable analysis of retinal characteristics

Using left-side stroke as the reference, the results from the multivariable logistic regression analysis of retinal characteristics are shown in Table 3. As shown in this table, two right-eye retinal characteristics and the retinal composite score were strongly associated with the stroke side. Patients with an increased bifurcation coefficient of arterioles in the right eye (RBCA) were at seven times higher risk of right-sided strokes, with an OR of 7.523 (95% CI, 1.823–31.044; P = 0.005). In addition, a higher value of bifurcation coefficient of venules in the right eye (RBCV) was also associated with a higher risk of right-side strokes, with an OR of 7.377 (95% CI, 1.771–30.724; P = 0.006). Furthermore, a retinal composite score including complex effects containing tortuosity, haemorrhage, and fractal dimension of the vessel network, were also positively associated with right-side stroke (OR, 4.955; 95% CI, 3.061–8.022; P < 0.001).

Table 3
Multivariable logistic regression for stroke sides.

	OR	**95% CI**	**p-Value**
RBCA	7.523	1.823–31.044	.005*
RBCV	7.377	1.771–30.724	.006*
Retinal Composite Score	4.955	3.061–8.022	< .001*

*p-Value < 0.05.

The area under the ROC curve was 0.842 (95% CI, 0.782–0.901) for the multivariate logistic regression with a sensitivity of 79.8% and specificity of 73.4% using a cutoff of 0.5 probability, indicating an excellent potential predictive ability. (Fig. 1)

Validation

The validation of the logistic model was performed via leave-one-out cross-validation. Using RBCA, RBCV, and retinal composite score, 76.2% of left-side strokes and 74.4% of right-side strokes were correctly classified with a total accuracy of 75.3%.

Discussion

Previous studies have revealed the association between retinal characteristics and stroke in many aspects, but here we further investigated the association of the brain side with stroke. It might be an effective way to reduce the burden by specifying the treatment according to the side of the stroke. Hence, identifying the stroke side was one of the critical roles. The current imaging tool and the gold standard would be MRI, but since it is an expensive and a time-consuming procedure, its use clinically and in research is limited. Other imaging tests, such as CT and angiography, help in identifying the location hours after strokes, but one of the problems using CT is the high radiation dose. Since the changes in retinal vessels can reflect some abnormalities in the cerebrovascular system, retinal characteristics might also provide information for diagnosis and treatment of brain diseases. To our knowledge, no study has investigated the association between retinal characteristics and stroke sides. Therefore, this study is the first to demonstrate that the eyes on one side might not correspond to the same side of the brain, but the retinal characteristics of both the eyes together would be able to determine the side of stroke. We further established a prediction model that may provide an additional source for stroke side identification. The retinal characteristics provided a classification of the left and right stroke sides with 76.8% accuracy based on the current study.

Our study found that an increased bifurcation coefficient for arterioles and venules was associated with a higher risk of right-side stroke, which indicated changes in the branching pattern of retinal vessels. In normal conditions, the pattern of retinal vasculature would provide an optimal route for blood flow with minimal energy costs. Although there is no literature available to support this finding, it might reflect that the side of the brain where the vessels are damaged by strokes could be identified via bifurcation coefficient in the retina. Since the biological effects are thought to be more complex, we explored the interactions between retinal characteristics. In this study, we found that as a series of retinal components increased at the same time, the risk of right-side stroke increased.

This study has several strengths and limitations. One of the major strengths of this study is that it is the first study to investigate the association between retinal characteristics and the stroke side and it also establishes a preliminary prediction model for identification. Some limitations should also be noted. First, the small sample size and missing values affect the statistical power of the model; for instance, exudate is a useful retinal parameter, but due to a large number of missing values, it cannot be presented in the model. In addition, a cross-sectional design makes it difficult for causal inferences. As a preliminary study, the underlying mechanisms for the associations are still unclear. In the future, we need to increase the sample size and design a better study model to investigate the issue. Moreover, to fulfil the need for clinical application, this model should also be validated.

Conclusion

In conclusion, our study provides an evidence of the association between retinal characteristics and stroke side. With the prediction model, in the future, we would be able to standardize the retinal image assessment automatically for the management of patients with stroke. This might be useful to improve the treatment and rehabilitation.

List Of Abbreviations

NIHSS – the National Institutes of Health Stroke Scale

BC – bifurcation coefficients

BA – bifurcation angles

CRAE – central retinal artery equivalent

CRVE – central retinal vein equivalent

AVR – arteriole-to-venule ratio

FD – fractal dimension

BCA – bifurcation coefficient of arterioles

BCV – bifurcation coefficient of venules

Declarations

Ethics statement

This study was approved by the Ethics Committee of the Shenzhen Traditional Chinese Medicine Hospital (approval number: 2018-75) and was performed in accordance with the guidelines of the Helsinki Declaration. All patients or their legal representatives provided written informed consent. The clinical trial registration number was ChiCTR1800019647.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LnJ, LeJ, ZB and ZY were involved in the study design. ZY and ZW acquired the date. YH, HX and WJ provided clinical assistance. LeJ and ZB calculated retinal characteristics using the ARIA system. LnJ, ZY, LeJ, and ZB prepared the draft of the manuscript. YZ and YH revised the manuscript. All authors have read and approved the final manuscript.

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Figures

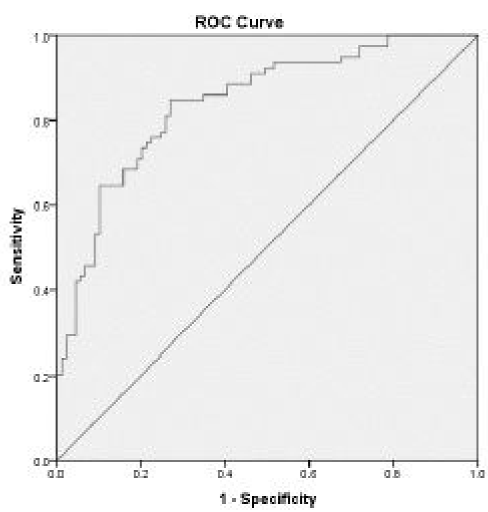

Figure 1

ROC curve of the multivariable logistic regression model for predicting stroke sides in patients.