Localized Retinal Nerve Fiber Layer Defects and Stroke

Dandan Wang, MD*; Yang Li, MD*; Chunxue Wang, MD; Liang Xu, MD; Qi Sheng You, MD; Ya Xing Wang, MD; Liang Zhao, MD; Wen Bin Wei, MD; Xingquan Zhao, MD; Jost B. Jonas, MD

Background and Purpose—Because the blood circulation system of retina and brain are closely related to each other, we examined whether stroke is associated with localized retinal nerve fiber layer defects (RNFLDs).

Methods—Patients with acute ischemic stroke as part of a hospital-based study group were compared with the participants of the population-based group Beijing Eye Study. The retina was imaged by spectral-domain optical coherence tomography for the detection of localized RNFLDs.

Results—The study included 154 patients with acute ischemic stroke and 2890 subjects from the Beijing Eye Study for whom optical coherence tomographic images of the retinal nerve fiber layer and data on a previous cerebral stroke were available. In logistic regression analysis, acute stroke was significantly associated with localized RNFLDs ($P<0.001$; odds ratio, 6.23; 95% confidence interval, 4.17–9.30) after adjusting for age, male sex, arterial hypertension, diabetes mellitus, and higher concentration of the C-reactive protein. In a similar manner, previous stroke was associated with localized RNFLDs ($P=0.04$; odds ratio, 1.48; 95% confidence interval, 1.02–2.16) in multivariate analysis. In a reverse manner, presence of localized RNFLDs was associated with cerebral stroke ($P<0.001$; odds ratio, 3.54; 95% confidence interval, 2.68–4.67) after adjusting for age, sex, and prevalence of diabetes mellitus.

Conclusions—Localized RNFLDs showed a strong association with previous or acute cerebrovascular stroke and vice versa after adjustment for other systemic and ocular factors. Localized RNFLDs that can be assessed by noninvasive optical coherence tomographic imaging may be added to the panoply of retinal morphological features of stroke. (Stroke. 2014;45:1651-1656.)

Key Words: stroke ■ tomography, optical coherence

The Global Burden of Disease (GBD) Study 2010 has shown that cerebrovascular stroke is one of the most common causes for disability-adjusted life-years lost and for death worldwide.1 Because the retina and its vascular system can be regarded as an extracranial part of the central nervous system, assessable by noninvasive ophthalmoscopy, numerous studies were focused on measuring the caliber of the retinal vessels and on assessing retinal microvascular abnormalities in patients who were at risk of, or who developed, a cerebrovascular stroke.2–11 Recent investigations have suggested that localized retinal nerve fiber layer defects (RNFLDs) may be an additional morphological retinal sign associated with the cerebrovascular status.12,13 To test the hypothesis of an association between localized RNFLDs and cerebrovascular stroke, we conducted this study in which we included a hospital-based study group of patients with acute stroke and compared it with a population-based group which was ethnically and regionally adjusted with the study group.

Methods

The hospital-based part of the study included patients who were consecutively diagnosed with an acute ischemic cerebral stroke between October 2011 and January 2013 in the Beijing Tiantan hospital. The study was performed according to the guidelines from the Helsinki Declaration and was approved by the Ethics Committee of the Beijing Tiantan hospital. Written informed consent was obtained from all participants. The diagnosis of ischemic stroke was based on the criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.14 All patients underwent a clinical neurological examination including blood sampling under fasting conditions at the first day after hospital admission for measurement of the blood concentrations of glucose, glycosylated hemoglobin, lipids, and C-reactive protein. In a structured interview, information was obtained on smoking habits differentiated into current smoking or former smoking (ie, no smoking for ≥5 previous years). Blood pressure was measured under standardized conditions. Arterial hypertension was defined as a systolic blood pressure ≥140 mm Hg, or a diastolic blood pressure ≥90 mm Hg, or self-reported current treatment for arterial hypertension with antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose concentration >7.0 mmol/L or 2 randomly examined
blood glucose concentrations >11.1 mmol/L or self-reported current treatment for diabetes mellitus with antihyperglycemic medication. Hyperlipidemia was defined as a blood cholesterol concentration >5.17 mmol/L, or blood concentration of triglycerides >1.7 mmol/L or a blood concentration of low-density lipoproteins >3.1 mmol/L. All patients additionally underwent spectral-domain optical coherence tomography (OCT; RTVue 100 OCT; Optovue Inc, Fremont, CA) of their retinal nerve fiber layer (RNFL). The OCT examination was performed within 7 days after the onset of stroke. The manufacturer’s Glaucoma Protocol, 3-D Optic Disc Protocol, and iWellness Protocol were applied to measure the circumpapillary RNFL thickness. An RNFLD was defined as a sector on the OCT printout in which the RNFL contour line dipped into the red zone for a length of <180° (Figure). A cerebral MRI examination (Veriomachine Siemens AG, Munich, Germany; slice thickness, 5/6 mm; field of view diameter, 240 mm; scan matrix, 156x156) was additionally performed for all patients within 14 days after the onset of stroke. Two neuroradiologists made the diagnoses of lacunar infarction, white matter lesions, and cerebral microhemorrhages using the Fazekas scale classification.14

The study group was compared with a control group that was formed from the population of the Beijing Eye Study 2011. The Beijing Eye Study 2011 was a population-based cross-sectional study in Northern China and was described in detail previously.15,16 Of an eligible population of 4403 individuals fulfilling the inclusion criterion of an age of 50+ years, 3468 (78.8%) individuals participated in the survey. The study design included an interview, a detailed ophthalmic examination, collecting of fasting blood samples, measurement of blood pressure, body height and weight, and spectral-domain OCT of the RNFL. The interview included detailed questions on a previous cerebral stroke including its date. All study participants were Han Chinese residing in Beijing.

The statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 21.0, IBM-SPSS, Chicago, IL). The analysis was performed in several steps as described below. Mean values were presented as mean±SD. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All P values were 2-sided and were considered statistically significant when the values were <0.05.

Figure. Spectral-domain optical coherence tomographic image (A) and the corresponding fundus photograph (B) of a localized retinal nerve fiber layer (RNFL) defect (white arrow in A; black arrows in B). INF indicates inferior region; NAS, nasal region; RNFLT, retinal nerve fiber layer thickness; SUP, superior region; and TMP, temporal region.
Results

The study group included 154 patients with a mean age of 57.1±12.1 years (range, 21–80 years; Table). Applying the TOAST classification, 60 (39%) patients belonged to the group of large artery atherosclerosis, 7 (5%) patients belonged to the group of cardioembolism, 44 (29%) patients belonged to the group of small artery occlusion, 4 (3%) patients belonged to the group of stroke of other determined cause, and 39 (25%) patients belonged to the group of stroke of undetermined cause.

As reported previously, 3368 of the 3468 participants of the Beijing Eye Study 2011 underwent the OCT examination.15,16 Because of unreliable RNFL measurements with respect to the detection of localized RNFLDs, 154 subjects were excluded, and data on previous stroke were not available for 150 additional subjects. Because glaucoma can lead to localized RNFLDs, we excluded all subjects (n=174) with glaucomatous optic neuropathy so that the study population provided by the Beijing Eye Study eventually included 2890 subjects (Table). The group of excluded subjects as compared with the group of subjects included into the study were significantly older (P<0.001) and were more likely to live in the rural region (P<0.001), whereas both the groups did not differ significantly in sex (P=0.85). In the group of the Beijing Eye Study, localized RNFLDs were detected in 350 subjects with a prevalence rate of 12.1±0.6% per eye (95% CI, 10.9–13.3) of participants of the Beijing Eye Study with previous stroke (P<0.001; OR, 0.92; 95% CI, 0.85–0.99), male sex (P<0.001; OR, 0.26; 95% CI, 0.17–0.40), arterial hypertension (P<0.001; OR, 3.01; 95% CI, 1.95–4.66), diabetes mellitus (P<0.001; OR, 2.42; 95% CI, 1.57–3.73), higher concentration of the C-reactive protein (P<0.001; OR, 1.09; 95% CI, 1.05–1.13), and localized RNFLDs (P<0.001; OR, 6.23; 95% CI, 4.17–9.30). We then formed a control group (n=1103 participants) which was matched for age (58.1±5.1 years [median, 58.0 years] versus 57.1±12.1 years [median, 58.0 years]) and prevalence of arterial hypertension (71.9±1.4% versus 75.3±3.5%) with the study group of patients with acute stroke. In multivariate logistic regression analysis, acute stroke was still significantly associated with localized RNFLDs (P<0.001; OR, 7.18; 95% CI, 4.65–11.1) after adjusting for male sex (P<0.001; OR, 0.26; 95% CI, 0.17–0.40), diabetes mellitus (P<0.001; OR, 2.36; 95% CI, 1.48–3.76), and higher concentration of the C-reactive protein (P<0.001; OR, 1.13; 95% CI, 1.07–1.19). Because of matching, the association with age (P=0.73) and arterial hypertension (P=0.96) was no longer statistically significant.

In the second step of the analysis, we compared the group of participants of the Beijing Eye Study with previous stroke with the group of participants of the Beijing Eye Study without previous stroke. In univariate analysis, previous stroke was significantly associated with older age (P<0.001), arterial hypertension (P<0.001), diabetes mellitus (P<0.001), higher level of glycosylated hemoglobin (P<0.001), and diabetic retinopathy (P<0.001) and localized RNFLDs (P<0.001). In multivariate logistic regression analysis with adjustment for blood concentrations of lipids and C-reactive protein, previous stroke remained significantly associated with male sex (P=0.01; OR, 0.63; 95% CI, 0.43–0.90), older age (P<0.001; OR, 1.05; 95% CI, 1.03–1.07), arterial hypertension (P<0.001; OR, 2.74; 95% CI, 1.78–4.21), diabetes mellitus (P=0.004; OR, 1.81; 95% CI, 1.21–2.70), and localized RNFLDs (P=0.04; OR, 1.58; 95% CI, 1.02–2.46).

In the third step of the analysis, we merged the hospital-based group and the Beijing Eye Study group. In multivariate logistic regression analysis, acute stroke combined with previous

<table>
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<tr>
<th>Parameter</th>
<th>Acute Stroke</th>
<th>P Value (1)</th>
<th>Previous Stroke</th>
<th>P Value (2)</th>
<th>No Stroke</th>
<th>P Value (2)</th>
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</thead>
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<tr>
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<td></td>
<td>206</td>
<td></td>
<td>2684</td>
<td></td>
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<tr>
<td>Age, y</td>
<td>57.1±12.1</td>
<td>&lt;0.001</td>
<td>70.4±9.0</td>
<td>&lt;0.001</td>
<td>63.6±9.3</td>
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<td>Men/women</td>
<td>116/38</td>
<td>&lt;0.001</td>
<td>108/98</td>
<td>0.007</td>
<td>1146/1538</td>
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<td>Arterial hypertension, %</td>
<td>75.3±3.5</td>
<td>&lt;0.001</td>
<td>80.6±2.8</td>
<td>&lt;0.001</td>
<td>51.5±1.0</td>
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<td>Diabetes mellitus, %</td>
<td>32.5±3.8</td>
<td>&lt;0.001</td>
<td>47.6±3.8</td>
<td>&lt;0.001</td>
<td>18.7±0.9</td>
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<td>Hyperlipidemia, %</td>
<td>40.3±4.0</td>
<td>0.26</td>
<td>50.1±3.9</td>
<td>0.001</td>
<td>35.6±1.1</td>
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</tr>
<tr>
<td>Smoking ever, %</td>
<td>59.0±4.0</td>
<td>&lt;0.001</td>
<td>30.0±3.2</td>
<td>0.94</td>
<td>30.0±0.9</td>
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<td>C-reactive protein, mg/L</td>
<td>4.19±4.96</td>
<td>&lt;0.001</td>
<td>1.98±2.46</td>
<td>0.74</td>
<td>1.91±3.59</td>
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<td>Glycosylated hemoglobin, %</td>
<td>6.36±1.42</td>
<td>&lt;0.001</td>
<td>4.61±1.28</td>
<td>0.01</td>
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<td>Diabetic retinopathy, %</td>
<td>5.2±1.8</td>
<td>0.02</td>
<td>28.4±2.0</td>
<td>&lt;0.001</td>
<td>20.2±0.3</td>
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<td>Retinal nerve fiber layer defect, %</td>
<td>48.1±4.0</td>
<td>&lt;0.001</td>
<td>40.7±2.8</td>
<td>&lt;0.001</td>
<td>11.4±0.6</td>
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<tr>
<td>Retinal vein occlusions, %</td>
<td>1.0±0.9</td>
<td>1.00</td>
<td>2.0±1.0</td>
<td>0.53</td>
<td>1.0±0.2</td>
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</table>

P value: Statistical significance of the difference between the group of patients with acute stroke and the group without stroke (P value [1]) or of the difference between the group of patients with previous stroke and the group without stroke (P value [2]).
stroke was significantly associated with localized RNFLDs (P<0.001; OR, 3.86; 95% CI, 2.79–5.34) after adjusting for age (P=0.005; OR, 0.98; 95% CI, 0.97–0.99), male sex (P<0.001; OR, 0.35; 95% CI, 0.26–0.47), prevalence of arterial hypertension (P<0.001; OR, 3.08; 95% CI, 2.21–4.30), diabetes mellitus (P=0.058; OR, 1.39; 95% CI, 0.99–1.95) and hyperlipidemia (P=0.03; OR, 1.40; 95% CI, 1.04–1.89), and higher concentration of C-reactive protein (P<0.001; OR, 1.08; 95% CI, 1.04–1.12).

In the fourth step of the analysis, we took the parameter of presence of localized RNFLDs as dependent variable. In univariate analysis, presence of localized RNFLDs was associated with higher age (P<0.001), male sex (P<0.001), arterial hypertension (P=0.001) and diabetes mellitus (P<0.001), and marginally with dyslipidemia (P=0.07) and with the prevalence diabetic retinopathy (P=0.02). In multivariate logistic regression analysis, presence of localized RNFLDs was significantly associated with acute or previous stroke (P<0.001; OR, 3.54; 95% CI, 2.68–4.67) after adjusting for older age (P<0.001; OR, 1.02; 95% CI, 1.01–1.03), male sex (P=0.002; OR, 0.69; 95% CI, 0.55–0.88), and presence of diabetes mellitus (P=0.03; OR, 1.36; 95% CI, 1.04–1.78). If the prevalence of stroke was dropped, the association between the prevalence of localized RNFLDs and arterial hypertension in the model was significant (P=0.005; OR, 1.41; 95% CI, 1.11–1.80). Similar results were obtained if acute stroke and previous stroke were analyzed separately. Presence of localized RNFLDs was significantly associated with acute stroke (P<0.001; OR, 7.25; 95% CI, 4.97–10.6) after adjusting for older age, male sex, and presence of diabetes mellitus and arterial hypertension. Presence of localized RNFLDs was significantly associated with previous stroke (P=0.02; OR, 1.68; 95% CI, 1.09–2.60) after adjusting for older age (P<0.001), male sex (P=0.02), diabetes mellitus (P=0.02), and more myopic refractive error (P<0.001).

Within the study group of patients with an acute cerebrovascular insult, the prevalence of localized RNFLDs was not significantly associated with the TOAST subgroups (P=0.71; ANOVA). The size of the TOAST subgroups was too small for meaningful statistical analysis of associations between the various morphological signs of cerebral ischemia and the prevalence of RNFLDs.

Discussion

Our investigation combining a hospital-based study group with a population-based group showed that acute or previous stroke was significantly associated with localized RNFLDs (P<0.001) after adjusting for parameters such as age, sex, arterial hypertension, and diabetes mellitus. In a reverse manner, presence of localized RNFLDs was significantly associated with cerebral stroke (P<0.001) in multivariate analysis. The findings suggest that localized RNFLDs may be added to the panoply of ophthalmoscopic features of stroke.

The results on the association of acute or previous stroke with localized RNFLDs as morphological abnormalities of the retina agree with that of previous studies. Retinal vascular abnormalities including localized and generalized arteriolar thinning, arteriovenous nicking, and a lower arteriolar/venular diameter ratio have been demonstrated to be significantly associated with eventual stroke and with arterial hypertension as one of the main risk factors for stroke.3–11 These studies on retinal microvascular abnormalities in >10000 subjects did not examine whether localized RNFLDs as another morphological marker were associated with arterial hypertension or with stroke. In contrast to retinal microvascular abnormalities, a localized RNFLD as detected on ophthalmoscopy or on conventional fundus photographs is an almost qualitative marker of abnormality because it usually does not occur in normal eyes.17,18 Retinal microvascular abnormalities, however, show a marked interindividual variability within the normal population and only a gradual transition from a normal status to a pathological status. The diagnostic specificity is therefore considerably higher for localized RNFLDs than for retinal microvascular abnormalities.

The results of the present study are in agreement with the findings of previous investigations in which spectral-domain OCT was applied to image the retina and to describe retinal changes, mainly in the RNFL of patients with Alzheimer disease, Parkinson disease, or schizophrenia.19–22 It suggests that spectral-domain OCT may be added to the retinal imaging diagnostic tests in patients with neurological disorders.

A previous study revealed that localized RNFLDs are associated with arterial hypertension.13 In that investigation, the ORs were higher for the association between arterial hypertension and localized RNFLDs than for the association between arterial hypertension and retinal microvascular abnormalities. Localized RNFLDs were also associated with the grading of arterial hypertension so that one assumed that the assessment of localized RNFLDs could be useful for the diagnosis and staging of arterial hypertension. These studies were in agreement with an investigation on arterial hypertensive rhesus monkeys, which developed localized RNFLDs during the follow-up.23 The results of our present study therefore extend these findings in that localized RNFLDs were not only associated with arterial hypertension but, more importantly, with one of the most important sequela of arterial hypertension, with stroke. It suggests that localized RNFLDs, in addition to the known retinal microvascular abnormalities, can be retinal markers of stroke. These findings were also parallel to the results of a study by Kim et al who reported an association between localized RNFLDs and cerebral small vessel disease.

Localized RNFLDs as a diagnostic marker have the distinct advantage that they remain visible as long as the surrounding RNFL has a sufficient height to create the spatial contrast to the localized RNFLD. It is in contrast to retinal vascular abnormalities, some of which, such as focal arteriolar narrowing, are partially reversible after reduction of arterial blood pressure.24 In analogy to lifelong detectable serum markers of some infectious diseases, such as syphilis, localized RNFLDs may be lifelong remnants of moderate or severe arterial hypertension if no other reasons for localized RNFLDs are present. A localized RNFLD usually develops as a consequence of a microinfarct in the RNFL. If ophthalmoscopically detectable, such a microinfarct has been called cotton-wool spot which remains visible for >2 months. One may assume that some patients with arterial hypertension and stroke have experienced microinfarcts of the RNFL which remained unnoticed because of their
usually negligible impact on visual acuity. Because the retinal vasculature belongs to the cerebral vascular system, retinal microinfarcts may have a parallel in cerebral microinfarcts and eventual stroke.

The detectability of localized RNFLDs depends on the thickness of the RNFL which in normal eyes is thickest in the temporal inferior sector and the temporal superior sector. The regional distribution in RNFL thickness is physiologically associated with the diameters of the retinal arterioles, with the physiological shape of the neuroretinal rim of the optic nerve head, and with the location of the foveola =0.5 mm inferior to the horizontal optic nerve head axis. The RNFL thickness physiologically decreases with older age, correlating with an age-related loss of ≈0.3% of the optic nerve fibers, retinal photoreceptors, and retinal pigment epithelium cells. Depending on these physiological parameters of the RNFL, localized RNFLDs are usually more often detected in the temporal inferior fundus region and temporal superior region than in other fundus areas. Localized RNFLDs can be caused by various ocular disorders such as glaucoma, optic disc drusen, and toxoplasmic retinochoroidal scars or caused by systemic diseases such as arterial hypertension and diabetes mellitus as shown in the present study. Although glaucomatous optic neuropathy as one of the most common causes of localized RNFLDs was an exclusion criterion for the present study, the prevalence of localized RNFLDs in the control group in our population-based study was 11.4% (Table). It showed that localized RNFLDs were not pathognomonic for stroke. The significant (P<0.001) difference in the prevalence of localized RNFLDs between the control group and the study group (11.4% versus >40%), however, revealed the strength of the association of localized RNFLDs with stroke in a general population which in addition to stroke naturally exhibited other disorders, leading to localized RNFLDs. From a clinical point of view, ocular diseases as causes for localized RNFLDs have to be taken into account in the differential diagnosis of localized RNFLDs as signs of arterial hypertension and stroke.

Potential limitations of our studies should be mentioned. First, the patients affected by acute stroke had been referred to the hospital so that a referral bias for this group could principally not be ruled out. If, however, only subjects of the Beijing Eye Study were included into the statistical analysis, preceding stroke was significantly associated with localized RNFLDs in univariate and in multivariate analysis. Second, the study was performed on Chinese patients who, because of variations in actual and previous lifestyle, may differ from patients in other countries.

From a practical point of view, the findings in our study suggest that retinal imaging, in our study by OCT, and assessment of the retinal microvascular abnormalities may be useful for the assessment of arterial hypertension and stroke as one of its sequelae.

Conclusions
Localized RNFLDs showed a strong association with previous or acute cerebrovascular stroke and vice versa after adjustment for other systemic and ocular factors. Localized RNFLDs that can be assessed by noninvasive OCT imaging may be added to the panoply of retinal morphological features of stroke.

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Disclosures
None.

References
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