Retinal microvascular abnormalities in different stroke subtypes: A cross-sectional study

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Abstract

Introduction This study aimed to describe retinal microvascular changes in patients diagnosed to have stroke and determine the association between retinal microvascular changes and type of stroke (lacunar and non-lacunar).

Methods This is a cross-sectional descriptive study conducted among stroke patients seen at the Neurology Ward and Neurology Out-Patient Clinic of the UERM Memorial Medical Center. The patients' demographic characteristics and risk factors were obtained through a standardized questionnaire. Retinal photographs of both eyes were taken in eligible patients who consented to join the study. Retinal vascular changes were identified and their association with the type of stroke was determined.

Results Thirty-seven patients, 64% of whom had small artery occlusion type of lacunar stroke, were enrolled in the study. The most prevalent retinal abnormalities for each type of stroke were AV nicking and focal arteriolar narrowing. The prevalence of abnormal retinal findings between patients with lacunar stroke and non-lacunar stroke were compared and showed insufficient evidence to demonstrate a statistical significance between abnormal retinal findings and lacunar stroke.

Conclusion There is no significant association between abnormal retinal findings and lacunar stroke.

Key words: Stroke, lacunar stroke, retinal vascular abnormality

Lacunar strokes, a disease of small perforating arteries 40-200 μm in diameter, are estimated to make up 25% of all ischemic strokes.[1-3] The etiology for this type of stroke remains elusive but some suggestions include atherothromboembolism, large intracranial artery stenosis, microvascular atheroma or endothelial dysfunction.[1] Lindley stated that there are three plausible pathologic mechanisms: 1) lipohyalinosis; 2) hyaline arteriosclerosis; and 3) microatheroma.[2]

Cerebral blood vessels and retinal vessels share structural similarities, having almost the same diameters (50-250 micrometers) and are both end arteries.[2,4] The two are also closely linked during embryologic development.[1] More importantly, they are known to be affected by identical vascular risk factors (i.e., hypertension and diabetes).[4] Thus, retinal

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vessel changes are likely to reflect similar changes in cerebral vessels.[5] The retinal vessel changes therefore have the potential to serve as markers for cerebral vascular disease and may provide clues in understanding cerebrovascular diseases such as stroke. The Atherosclerosis Risk in Communities Study (ARIC) showed that generalized arteriolar narrowing and generalized venular widening correlated with incident lacunar strokes.[5] This study aimed to describe retinal microvascular changes in patients diagnosed to have stroke and determine the association between retinal microvascular changes and type of stroke (lacunar and non-lacunar).

Methods

This is a cross-sectional descriptive study conducted among stroke patients seen at the Neurology Ward and Neurology Out-Patient Clinic of the UERM Memorial Medical Center from July to September 2016. Retinal photographs of both eyes were taken in eligible patients who consented to join the study. Retinal vascular changes were identified and their association with the type of stroke was determined. The study was approved by the Ethics Review Committee of the Medical Center.

Male or female pay or service patients above 18 years diagnosed to have a stroke in the past year, whether first episode or not, with or without risk factors for stroke, admitted at the Neurology Ward or consulting at the Neurology Out-Patient Clinic were recruited. An informed consent was obtained from those who agreed to join the study. Those who were comatose or medically unstable, could not tolerate retinal imaging, had a history of ocular trauma or whose retinal photographs could not be evaluated (due to media opacities or small pupils) were excluded. Stroke cases that were cryptogenic, or due to hypercoagulable, inflammatory causes, and cerebrovascular bleeds due to arteriovenous malformation or subarachnoid hemorrhage were likewise excluded. A sample size of 91 patients was initially calculated for this study, with 80% power to detect an effect size of 0.72 based on a study by Baker at 0.05 α-level of significance.[3] However, due to the number of patients admitted or seen at the Out-Patient Clinic (20 patients per month), the computed sample size was adjusted accordingly. Given an estimated population size of 60, the sample size was adjusted to 37.

A standardized questionnaire used to obtain the subject's demographic data and risk factors for stroke was filled up by the neurology resident. A neurological examination was performed on all patients. Strokes were classified as ischemic or intracerebral hemorrhage. Ischemic strokes were further classified into large artery atherosclerosis, cardioembolism and small artery occlusion based on the TOAST Classification.[6] Small artery occlusion and cardioembolism were categorized as lacunar stroke, while large artery atherosclerosis and cerebrovascular bleed, as non-lacunar stroke. The following risk factors were identified: hypertension, type 2 diabetes, prediabetes, coronary artery disease, dyslipidemia, smoking and frequent alcohol intake. These factors were defined as appropriate to the requirements of the study.[7]

A 45-degree non-mydriatic retinal photograph of both eyes centered on the optic disc and macula was taken using a Zeiss FP-450 IRU Fundus Camera with Visupac System (220vac) 430c and printed using photo-paper, providing documentation of the optic disc, macula, substantial portions of the temporal arcades, and about two disc diameters of retina nasal to the optic disc. The ophthalmology resident, blinded to the type of stroke, read the photographs and identified specific retinal findings based on the Atherosclerosis Risk in Communities Carotid (ARIC) MRI Study Retinal Photograph Grading Protocol.[8] Specific parts of the ARIC Grading Form were simplified and used to grade the retinal microvascular abnormalities. A retinal specialist confirmed the accuracy of the findings. Patients with a fundus photograph judged to have a treatable pathologic condition that posed an imminent threat to vision were referred to a retinal specialist for appropriate management.

The retinal photograph was viewed under a fluorescent lamp 14 inches away from the table where the photo was read. A grid produced on a transparent film was overlaid on the retinal photograph. The grid had three circles outlining an average disk, the zone from the disk margin to 0.5 disk diameter (DD) from the disk margin (Zone A), and from 0.5 DD to 1 DD from the disk margin (Zone B). Four lines radiating from the central circle were used to divide the part of the photograph outside zone A into four quadrants centered on the disk: superior temporal, superior nasal, inferior nasal, and inferior temporal (Figure 1). Retinal microvascular changes were identified by the photograph reader without the aid of a computer program.

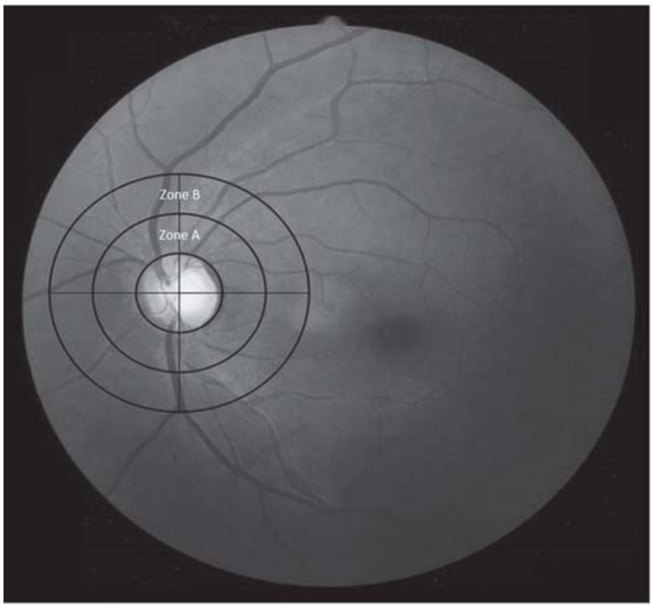

Figure 1. Retinal photograph grid

The specific retinal microvascular changes of interest and their definitions were: 1) arterial focal narrowing - marked constrictions located at Zone A and Zone B defined as a constricted artery that has a caliber less than or equal to 1/2 the caliber of proximal and distal vessel segments; 2) arterio-venous nicking (AV nicking) - arterio-venous crossings found outside of Zone A where tapering or narrowing of both sides of the venous blood column occurs as it crosses an artery; arterial sheathing; greyish or whitish sheath enveloping retinal vessels; 3) microaneurysms - described as typically round, red capillary ballooning, usually having smooth margins and a diameter of less than 150 um; 4) hemorrhage - encompassing blot and flame-shaped hemorrhages; blot hemorrhages appearing as slightly larger than microaneurysms, which may or may not have distinct borders; flame-shaped hemorrhages occur over the retinal fiber layer, coursing through the pattern giving it its flame/splinter-like shape; 5) hard exudates - lipid deposits within the retina, characteristically bright yellow-white deposits with sharp margins, appearing waxy, shiny, or glistening, arranged as individual dots, confluent patches, or in rings surrounding zones of retinal edema and/or groups of microaneurysms; 6) soft exudates - indicating areas of ischemia in the retina appearing as superficial white, pale yellow-white or grey-white areas with feathery edges, frequently showing striations parallel to the nerve fibers; soft exudates were graded as present or absent; 7) intraretinal microvascular abnormalities (IRMA) - tortuous intraretinal vascular segments varying in caliber; may be difficult to distinguish IRMA from new vessels; in general, IRMA are more delicate, more angular or jagged in their tortuosity, less likely to cross themselves or other retinal vessels, and more likely to occur in relatively open areas between major vessels; 8) venous beading (VB) - referring to localized increases in the venous caliber (segmental dilation), sometimes resembling a string of beads; 9) new vessels on the disc (NVD) - new vessels originating on the surface of the optic disc or on the retina within 1 DD of the disc margin (Zone B) or in the vitreous cavity anterior to this area. New vessels originating elsewhere but extends within 1 DD were considered as NVE; 10) new vessels elsewhere (NVE) - any new vessels on the surface of the retina or further forward in the vitreous cavity were considered new vessels elsewhere.[8]

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and IQR for ordinal variables, and mean and SD for interval/ratio variables. A p-value ascertained whether any baseline differences existed between the two groups. Independent sample T-test, Mann-Whitney U test and Fisher's exact/chi-square test were used to determine the difference of mean, median and frequency between groups, respectively. Odds ratios and the corresponding 95% confidence intervals were computed to determine the association of retinal microvascular abnormalities to the occurrence of lacunar and non-lacunar stroke. STATA 12.0 was used for data analysis.

Results

Thirty seven (37) stroke patients in this study with a mean age of 55.9 years consisting of a similar number of men and women. Almost two-thirds had a lacunar small artery occlusion type of stroke; among the non-lacunar strokes, there were three times more cerebrovascular bleeds. Hypertension was the most common comorbidity in both lacunar and non-lacunar types of stroke. A family history of stroke was the most common risk factor in both lacunar and non-lacunar strokes (Table 1). No correlation between the risk factors and stroke types was identified, however there was a statistically significant association between diabetes mellitus and large artery atherosclerosis and small artery occlusion.

The prevalence of specific retinal abnormalities for each type of acute stroke are shown in Table 2. AV nicking was among the most common retinal finding in both lacunar and non-lacunar stroke followed by focal arteriolar narrowing. The authors compared the prevalence of abnormal retinal findings between patients with lacunar strokes versus non-lacunar types. The odds of abnormal retinal findings among lacunar stroke patients was 2.4 and 5.5 for non-lacunar stroke patients. However, there was insufficient evidence to demonstrate a statistically significant association between lacunar and non-lacunar type strokes and retinal abnormalities (p = 0.44), as seen in Table 3.

Discussion

Certain retinal findings have been associated with cerebrovascular accidents in several large-scale studies. The Atherosclerosis Risk in Communities (ARIC) Study established that patients with hypertensive retinopathy findings such as microaneurysms, hard and soft exudates, and retinal hemorrhages were significantly more likely to have MRI-detected silent cerebral infarcts.[4] Furthermore, it reported that focal arteriolar narrowing, enhanced arteriolar light reflex, AV nicking, and widening of retinal venules were common in patients with lacunar infarction.[3] With the different stroke types combined, the most frequent retinal microvascular abnormalities seen in this study are focal arteriolar narrowing and AV nicking, both of which are early signs of hypertensive retinopathy. In the present study, 56.5% of the patients with lacunar stroke had arteriovenous nicking while 30.4% have focal

Table 1. Clinical characteristics of 37 patients diagnosed with acute stroke at UERM Medical Center.

Characteristic	Lacunar stroke: Small artery occlusion (n=23)	Lacunar stroke: Cardioembolism (n=1)	Non-lacunar strokes: Large artery atherosclerosis (n=3)	Non-lacunar strokes: Cerebrovascular bleed (n=10)	P-value
	Frequency (%); Mean ± SD; Median (Range)				
Age (yr)	55.5 (33-75)	49	53 (28-60)	58.5 (45-69)	0.37*
Sex					1.00+
Male	11 (47.8)	1 (100)	2 (66.7)	5 (50)	
Female	12 (52.2)	0	1 (33.3)	5 (50)	
Educational attainment					0.05+
Below college	19 (82.6)	1 (100)	1 (33.3)	10 (100)	
College	4 (17.4)	0	2 (66.7)	0	
Comorbidities					
Hypertension	15 (65.2)	1 (100)	2 (66.7)	7 (70)	1.00+
Diabetes mellitus Type 2	15 (65.2)	0	1 (33.3)	0	<0.01+
Dyslipidemia	13 (56.5)	1 (100)	1 (33.3)	3 (30)	0.41+
Hypertension					
SBP (n=17)	130 (120-170)	-	135 (120-150)	130 (120-180)	0.92*
DBP (n=17)	90 (70-100)	-	60 (40-80)	80 (80 to 150)	0.25*
Smoking History	8 (36.4)	1 (100)	1 (33.3)	3 (30)	0.78+
Cardiovascular History*					
Angina	3 (13.0)	1 (100)	0	0	0.10+
Atrial fibrillation	6 (26.1)	0	1 (33.3)	2 (20)	1.00+
Family history of stroke	11 (47.8)	1 (100)	0	5 (50)	0.35+
Previous stroke	6 (26.1)	0	1 (33.3)	2 (20)	1.00+

Table 2. Prevalence of retinal abnormality among patients diagnosed with acute stroke at UERM Medical Center, 2016.

	Lacunar stroke		Non-lacunar strokes	
Retinal change	Small artery occlusion (n=23)	Cardioembolism (n=1)	Large artery atherosclerosis (n=3)	Cerebrovascular bleed (n=10)
	Frequency (%)			
Absent retinal findings	6 (26.1)	0	2 (66.7)	1 (10)
Focal arteriolar narrowing	7 (30.4)	1 (100)	1 (33.3)	4 (40)
AV nicking	13 (56.5)	0	1 (33.3)	7 (70)
Arteriolar sheathing	2 (8.7)	0	1 (33.3)	0
Hard exudates	2 (8.7)	0	1 (33.3)	0
Hemorrhages	3 (13.0)	0	0	1 (10)
Microaneurysms	2 (8.7)	0	0	2 (20)
Soft exudates	2 (8.7)	0	0	1 (10)
NVD	2 (8.7)	0	0	0
Venous beading	1 (4.4)	0	0	0
Tortuous veins	0	0	0	0
IRMA	0	0	0	0
NVE	0	0	0	0

Table 3. Association between lacunar strokes and abnormal retinal findings.

	Lacunar stroke (n=24)	Non-lacunar stroke (n=13)	Odds Ratio (95% CI)	P-value
	Frequency (%);			
With abnormal retinal findings	17 (70.8)	11 (84.6)	0.44 (0.04 - 3.00)	0.45
Without retinal findings	7 (29.2)	2 (15.4)		

arteriolar narrowing. This high frequency of focal arteriolar narrowing and AV nicking in lacunar strokes is similar to the findings of Yatsuya, which showed a significant association.[5] The results did not show a significant association. Thus, this study could not conclude that retinal microvascular changes are particular for lacunar strokes. The results were also different in that even non-lacunar strokes (particularly bleeds) showed a predominance of focal arteriolar narrowing and AV nicking.

The results on focal arteriolar narrowing and arteriovenous nicking were similar results to those of Cooper.[4] Subjects in Cooper's study however did not manifest with clinical stroke but instead had "silent strokes" detected on MRI. This investigation, on the contrary, included patients who already sustained clinical strokes. A prospective study showed that focal arteriolar narrowing and AV nicking were the retinal findings found to be most associated with stroke; the association was significant.[4]

For this study, the high occurrence of focal arteriolar narrowing and AV nicking in all stroke types in general, and not to lacunar strokes in particular, may be related to the co-morbidities of stroke. It had been previously claimed that these two particular retinal microvascular abnormalities are associated with hypertension as well as atherosclerosis.[9] In line with this, hypertension, as known, is not particular to lacunar strokes but is associated with all strokes in general, including hemorrhages. Thus, it would be difficult to claim that presence of focal arteriolar narrowing and AV nicking would predispose one to a particular stroke type, i.e., lacunar stroke. It could only be said that these microvascular abnormalities are small vessel manifestations of hypertension and a general state of atherosclerosis. While hypertension has a strong association with lacunar strokes, studies have shown only a marginal excess of hypertension in the lacunar type of stroke versus non-lacunar types.[9] This could explain why both lacunar and non-lacunar strokes, by having hypertension as a common comorbidity, would present with such hypertension-related microvascular changes.

These two retinal findings are microvascular abnormalities that, in previous studies, have been strongly correlated with hypertension.[4] In this study's population, majority of the lacunar stroke patients were hypertensive. The other types of strokes also show hypertension as a prevalent risk factor, especially bleeds where 70% were hypertensive. This study did not further evaluate whether the increased frequency of focal arteriolar narrowing and AV nicking in lacunar and non-lacunar strokes is an effect of hypertension rather than as an independent risk factor of the stroke type. Focal arteriolar narrowing, in particular, has a high association with hypertension, specifically with present blood pressure elevations. It results when autoregulation fails, and the arteriolar pressures reach 130-160 mmHg. This uncontrolled increase in blood pressure causes structural damage in the intima of the arteriolar wall. The overall result is breakdown of the blood-retina barrier.[3] However, although there is a pathophysiology explaining the effect of hypertension on retinal vessels, there are other variables that are contributory. These include genetic, embryologic, environmental and lifestyle factors such as diet. It has been further suggested that these factors may modify the effect of hypertension on microvascular circulation.[10]

Among the comorbidities for cardiovascular disease evaluated in this study, it is diabetes mellitus that is significantly associated with all stroke types. Diabetes mellitus, by promoting atherosclerosis in both large and small arteries, increases stroke risk by as much as two times.[7] The ARIC study has found that there is a six-fold higher risk of incident stroke, and a two-fold higher risk of stroke mortality in people with type 2 diabetes.[10,11] In this study, the mild non-proliferative diabetic retinopathy finding of retinal microaneurysms was present only in 8.7% of lacunar stroke in patients with small artery occlusion, and 20% in patients with cerebrovascular bleeds.

For this study, there was a higher frequency of abnormal retinal findings in the non-lacunar type (84.6 vs 69.6%) although this was not significant. Thus, a true microvascular link with non-lacunar or lacunar strokes could not be made. This is in strong contrast to a study which showed that retinal microvascular abnormalities are particular for lacunar stroke.[4] The latter study even made a suggestion that indeed, microvascular pathways were more important for lacunar stroke. Such cannot be said when the present study's results are interpreted. There is one study, however, showing focal arteriolar narrowing and AV nicking to be more common in intracerebral hemorrhage (deep penetrating type) as compared to lacunar stroke.[3] These results are similar to this study. Arteriolar narrowing had an odds ratio of 3.7 while AV nicking had a ratio of 2.6, in relation to cerebral bleeds. Deep penetrating hemorrhages, just like lacunar infarcts, involve small vessels; thus, it is likely that retinal microvascular abnormalities are also common to deep cerebral hemorrhages which often involve small vessels. In this study, for the intracerebral bleeds, 70% had AV nicking while 40% had focal arteriolar narrowing. It must be noted though that in this study, the intracerebral bleeds were not further classified into small, deep penetrating versus large vessel cortical bleeds. In future studies, the authors suggest that such classification of bleed be made.

Although the present study did not yield significant associations between stroke type and specific retinal microvascular abnormalities, it did show a high prevalence of the latter in stroke in general. Though for this study, retinal abnormalities did not seem to predict stroke type, future cohort studies examining retinal photographs and retinal microvascular changes in patients with risks for stroke is a notable endeavor. A limitation of this study is the sample size: although the calculated sample size was achieved, increasing this number could have resulted to more significant associations and better representation of all stroke types. Another limitation of this study was its cross-sectional design: because the sample taken were patients who had already stroked out, a cause and effect relationship could not be made. Hence, one could not infer from this study whether retinal microvascular changes preceded, hence predict, future stroke. Only associations could be made, at the least, and such was not shown in this study.

This investigation also raises the question on whether all stroke patients should undergo routine ophthalmologic examination. While no concrete associations have been made, findings of retinal microvascular abnormalities in majority of lacunar and non-lacunar strokes (84.6 and 70.8%) provide some basis for advocating such practice. However, when such retinal microvascular abnormalities are determined, they may simply serve as reflections of the patient's comorbidities such as hypertension, diabetes, and atherosclerosis. It remains uncertain whether they may predict future cardiovascular events. To answer this, an investigation with a prospective design is probably indicated.

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