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Retinal micro-vascular changes in acute stroke patients using funds photography

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Abstract
Objective: The aim of this study was to examine the retinal micro-vascular changes in acute stroke patients and their correlation with severity of stroke.
Methods: In this prospective study 50 patients with acute stroke were enrolled. Stroke was diagnosed by neurologist based on clinical features, physical signs and radiological imaging. Grading of stroke was done by using ICH grading score and NIHSS grading. Retinal photographs of 4 fields (optic disc, macula, superior arcade, and inferior arcade) of each eye were captured by using a digital retinal funds camera (Carl Zeiss Meditec AG FF 450 plus) and were assessed for following micro-vascular changes: Retinal vascular tortuosity, Retinal vascular caliber, Focal arteriolar narrowing, AV nicking, soft exudates and hard exudates.
Results: In this study, funds findings were present in 48 (96%) patients. 92.31% patients of Ischemic stroke, 100% patients of Hemorrhagic stroke and lacunar stroke had generalized arteriolar narrowing. About 64.29% patients of Hemorrhagic stroke, 61.54% ischemic stroke patients and 100% lacunar stroke patients had Focal arteriolar narrowing. About 50% Hemorrhagic stroke patients, 34.62% Ischemic stroke patients and 100% lacunar stroke patients had AV nicking. About 1% Ischemic stroke patients, 100% lacunar stroke patients had hard and soft exudates. Mean AV ratio in Hemorrhagic, Ischemic and Lacunar stroke was 0.564 mm, 0.592 mm and 0.400 mm respectively.
Conclusion: Our study demonstrated that, there is a strong association between retinal micro-vascular changes and cerebral microvasculopathy leading to stroke. We also found significant correlations between retinal micro-vascular changes and severity of the stroke.

Keywords: Stroke, retina, funds, digital funds camera, microvascular changes, correlation

Introduction
Stroke is defined as an abrupt onset of focal neurological deficit that is attributable to a vascular cause. Stroke is the second leading cause of death worldwide [1] and places a remarkable burden on families and society. In the clinic, stroke is presented in two major forms: ischemic stroke (IS) and hemorrhagic stroke (HS), of which ischemic stroke accounts for 65% [2]. Stroke is the most common manifestation of cerebrovascular disease. The presenting features include unilateral weakness, speech disturbances, visual deficit, visuo-spatial dysfunction, ataxia, headache and seizure.
Micro-vascular damage (in cerebral vessels) of stroke patients has been implicated in the pathogenesis of stroke [3, 4]. The inner retina microvasculature provides a route to assess the cerebral microvasculature directly and non-invasively *in vivo*, because reports have shown that the retinal microvasculature shares similar physiological, embryological, and anatomical features with the cerebral microvasculature [5, 6]. The retina is an extension of diencephalon and possesses blood - retinal barrier that is analogous to blood - brain barrier. Changes in the retinal vessels reflect similar changes in cerebral vessels. Thus studying retinal signs may provide clues to understanding the pathophysiology of stroke [7, 8].
In the past few years, there has been increasing evidence that the traditional indicators of retinal micro-vascular damage such as retinal vascular caliber changes and arteriolar narrowing are associated with cerebrovascular diseases including stroke. Although some clinicians recognize these retinal signs on examination with an ophthalmoscope, they are usually too subtle to be detected reliably this way. Nowadays, the retinal micro-vascular abnormalities on funds during stroke can be visualized, quantified and monitored non-invasively using funds photography with a funds camera.
Ocular funds photography is the classic imaging technique to capture photography of the retina. It is rapid and inexpensive imaging modality which provides high resolution, 2-D

cross-sectional images [9-11]. The optical design of funds cameras is based on the principle of monocular indirect ophthalmoscopy. A typical camera views 30 to 50° of retinal area, with a magnification of 2.5x. The retina can be imaged directly as the pupil is used as both the entrance and exit for the camera's illuminating and imaging light rays. Ocular funds photography can capture different types of retinal vascular signs as qualitative retinopathy, retinal arteriolar signs and changes in the retinal vascular caliber [12, 13].

The purpose of our study was to examine the retinal micro-vascular changes in acute stroke patients and their correlation with severity of stroke. Various retinal micro-vascular changes i.e., retinal vascular tortuosity, retinal vascular caliber measurements, AV nicking, soft and hard exudates were assessed which could be regarded as the risk markers for stroke.

Methods

This prospective study was conducted in the Postgraduate Department of Ophthalmology in collaboration with Department of Medicine, over a period of one and a half year. After obtaining ethical clearance from institutional ethics committee, 50 patients with acute stroke presenting to medicine emergency were enrolled in this study. Patients who fulfilled the following criteria were included in the study and informed consent was taken from each patient after explaining the purpose of the study.

The inclusion criteria were: any patients with acute stroke and patients willing to participate in the study. Unconscious patients, Patients with history of ocular trauma, old retinal vascular occlusion, diabetes, glaucoma, blindness, breastfeeding and pregnant women were excluded from this study.

Stroke was diagnosed by neurologist based on clinical features, physical signs and radiological imaging. Wegner and Keith grading of hypertensive retinopathy was used to compare grade of hypertensive retinopathy with the severity of stroke [14, 15]. Grading of stroke was done by using ICH grading score and NIHSS grading.

Demographic information, medical history and medication usage was taken. Patients underwent a complete ophthalmological examination including best corrected visual acuity (BCVA), Slit Lamp examination, IOP determination. Funds were examined by slit lamp bio microscopy using 78D lens and indirect ophthalmoscopy.

Retinal photographs of 4 fields (optic disc, macula, superior arcade, and inferior arcade) of each eye were captured by using a digital retinal funds camera (Carl Zeiss Meditec AG FF 450 plus) and were assessed for following micro-vascular changes: Retinal vascular tortuosity, Retinal vascular caliber, Focal arteriolar narrowing, AV nicking, soft exudates and hard exudates. AV ratio was measured manually using the calibrated scale of funds camera from retinal arteries and veins within two disc diameter from optic disc (Figure 1).

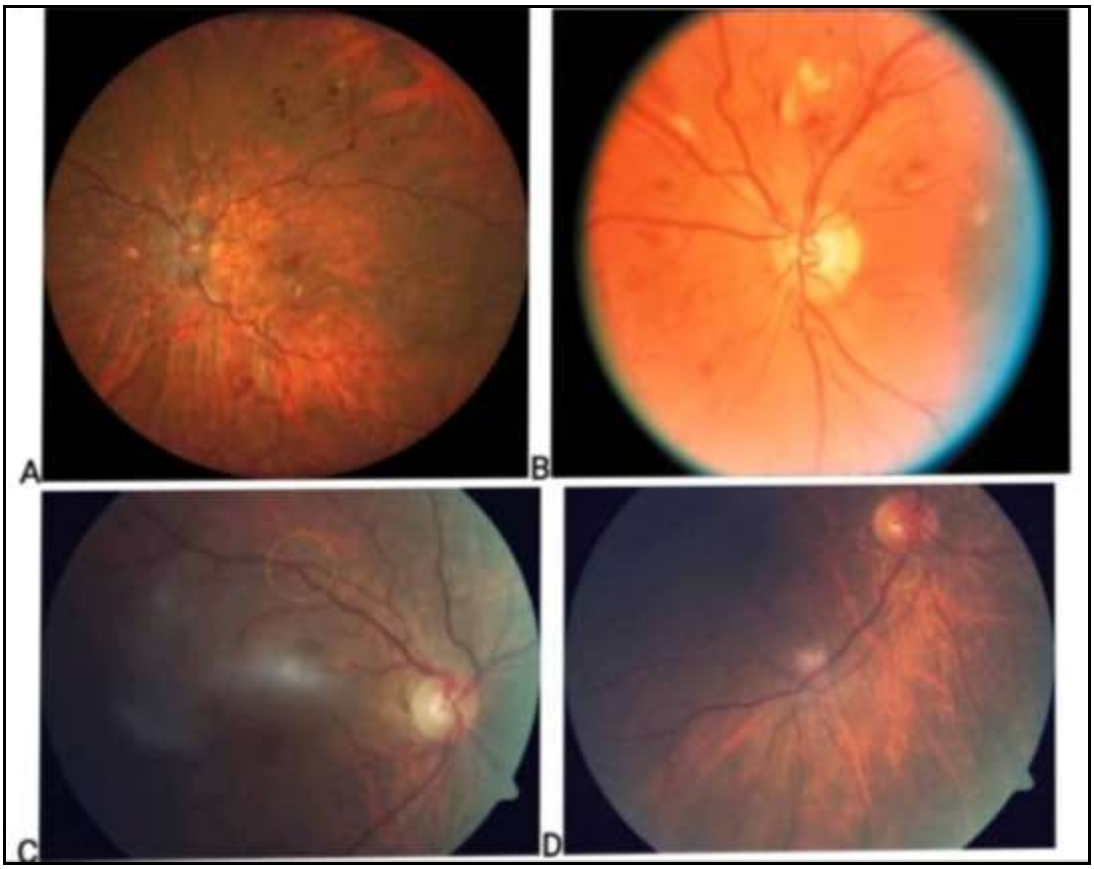

Fig 1: A (Funds photo showing generalized arteriolar narrowing), B (Funds photo showing Soft Exudates), C (Funds photo showing Arteriovenous nicking) and D (Arteriolar and Venous diameter measurement)

Results

The mean age of the patients was 65.19 ± 9.42 (range 50-90) years in this study. Among 50 patients there were 27 (54%) males and 23 (46%) females. In this study 14 (28%) patients had Hemorrhagic stroke, 26 (52%) Ischemic stroke and 10 (20%) had lacunar stroke. 11 (22%) patients had grade 1 stroke, 27 (54%) had grade 2, 11 (22%) had grade 3 and 1 (2%) had grade 4 stroke (Table 1).

Table 1: Demographic and baseline characters of patients

Demographic characters		No. of patients	Percentage
Gender	Male	27	54
	Female	23	46
Type of stroke	Hemorrhagic	14	28
	Ischemic	26	52
	Lacunar	10	20
Grade	Grade I	11	22
	Grade II	27	54
	Grade III	11	22
	Grade IV	1	2

In this study, funds findings were present in 48 (96%) patients. Among these findings, generalized retinal arteriolar narrowing was most common, present in 48 (96%) patients followed by focal arteriolar narrowing and arteriovenous nicking in 35 (70%) patients and 26 (52%) patients respectively. Hard and soft exudates were present in 9 (18%) patients.

In this study, 92.31% patients of Ischemic stroke, 100% patients of Hemorrhagic stroke and lacunar stroke had generalized arteriolar narrowing. About 64.29% patients of Hemorrhagic stroke, 61.54% ischemic stroke patients and 100% lacunar stroke patients had Focal arteriolar narrowing. About 50% Hemorrhagic stroke patients, 34.62% Ischemic stroke patients and 100% lacunar stroke patients had AV nicking. About 1% Ischemic stroke patients, 100% lacunar stroke patients had hard and soft exudates. In this study mean AV ratio in Hemorrhagic and Ischemic stroke was 0.564 mm and 0.592 mm respectively, with statistically significant p value with respect to baseline of <0.05. Mean AV ratio in Lacunar stroke patients was 0.400 mm that is statistically significant with p value of 0.001 (Table 2).

Table 2: Correlation between severities of stroke and of retinal micro-vascular changes

Parameters	Hemorrhagic (N=14)	Ischemic (N=26)	Lacunar (N=10)
Generalized retinal arteriolar narrowing			
Present (%)	14 (100%)	24 (92.31%)	10 (100%)
Absent (%)	0 (0%)	2 (7.69%)	0 (0%)
Focal arteriolar narrowing			
Present (%)	9 (64.29%)	16 (61.54%)	10 (100%)
Absent (%)	5 (35.71%)	10 (38.46%)	0 (0%)
Arteriovenous nicking			
Present (%)	7 (50%)	9 (34.62%)	10 (100%)
Absent (%)	7 (50%)	17 (65.38%)	0 (0%)
Hard and soft exudates			
Present (%)	0 (0%)	1 (3.85%)	8 (80%)
Absent (%)	14 (100%)	25 (96.15%)	2 (20%)
Arteriovenous ratio (Mean ± SD) mm	0.564±0.1336	0.592±0.1324	0.400±0.1054

Discussion

Retina is considered an extension of the brain and thus serves as a gateway to the brain. Retinal vessels offer a unique "window" to non-invasively investigate the change of the microcirculation in cerebrovascular diseases because retinal vasculature shares many common anatomical and physiological characteristics with the cerebral vasculature [16-18]. In this study, we used funds photography to evaluate the retinal vasculature in stroke patients and their correlation with severity of the stroke.

In this study, we evaluated 50 patients of acute stroke. Among them, 26 patients had ischemic stroke (large vessel stroke), 14 patients had Hemorrhagic stroke and 10 patients had Lacunar stroke with mean age of 61.58, 64.29 and 69.70 years respectively, (range 50-90) years. The possible reason for this is that the incidence of stroke increases with age due to atherosclerotic changes in vessels which is mainly responsible for stroke. This is consistent with the study done by Michelle *et al* [19], where patients had a range of 67-97 years of age. This finding is supported by other studies also which showed that stroke is commonly seen in elderly patients. Our study group consisted of 27(54.0%) males and 23 (46.0%) females, consistent with the studies done by De Silva *et al*. [20] there were 58% males and 42% females and Abah *et al*. [21] there were 59.6% males and 40.4% females. Whereas in study by Uhumwangho *et al*. [22] who reported 61 males (71.8%) and 24 females (28.2%).

In our study, the patients of stroke irrespective of the type of stroke had retinal microvascular changes. Generalized arteriolar narrowing was seen in 14 (100%) of Hemorrhagic stroke, 10 (93.4%) patients of Ischemic stroke (large vessel stroke) and 10 (100%) patients of lacunar stroke. Focal arteriolar narrowing was seen in 70% of patients, AV nicking was seen in 52% of patients and Hard, soft exudates in 18% of patients. This is consistent with the study done by Emmanuel *et al* [23] where 16.5% of patients had hard and soft exudates, 54.7% of patients had AV nicking. In this study, patients with lacunar stroke were more likely to have retinal micro-vascular signs as compared to other stroke types. Focal arteriolar narrowing was present in 9 (63.3%) patients of Hemorrhagic stroke, 16 (61.5%) patients of Ischemic stroke (large vessel stroke) and 10 (100%) patients of lacunar stroke. AV nicking was present in 7 (50%) patients of Hemorrhagic stroke, 9 (34.6%) patients of Ischemic stroke (large vessel stroke) and 10 (100%) patients of lacunar stroke. This was consistent with the study done by Michelle *et al* [19] where 80% of lacunar stroke patients among the types of stroke had more micro-vascular changes than other types.

In our study, the mean arteriovenous ratio (AVR) in lacunar, hemorrhagic and ischemic stroke patients was 0.400 mm, 0.564 mm and 0.592 mm. Hence, AVR was lowest in lacunar stroke patients with significant p value (<0.01). This is consistent with the study done by Richard *et al* [24], where the lacunar stroke patients had a mean AVR of 0.6mm with a significant p value < 0.0001. In our study, 8(80%) patients of lacunar stroke had hard and soft exudates as compared to 1% and 0% in Hemorrhagic and Ischemic stroke (large vessel stroke) patients respectively. This was not consistent with any other studies.

Our study suggests that retinal micro-vascular abnormalities in stroke can be reliably detected and accurately quantified by using funds photography with a funds camera, which is noninvasive and cost-effective without the radiation

exposure from CT or the invasive operation from DSA. It is rapid and inexpensive imaging modality which provides high resolution, 2-D cross-sectional images. The retina can be imaged directly as the pupil is used as both the entrance and exit for the camera's illuminating and imaging light rays. Ocular funds photography can capture different types of retinal vascular signs as qualitative retinopathy, retinal arteriolar signs and changes in the retinal vascular caliber.

Our study demonstrated that, there is a strong association between retinal microvascular changes and cerebral microvasculopathy leading to stroke. We also found significant correlations between retinal micro-vascular changes and severity of the stroke. Patients with lacunar stroke are more likely to have a range of retinal microvascular changes (Arteriolar narrowing, Arteriovenous nicking, Hard and soft exudates, Smaller Arteriovenous ratio) than other types of stroke.

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Author's contribution

Dr. Aisha Ashraf: concept, study design, literature search, statistical analysis, data acquisition and manuscript preparation

Dr. Sabia Rashid: definition of intellectual content, data acquisition, manuscript editing, statistical analysis and manuscript review

Dr. Irfan Yousuf: study design, clinical studies and manuscript preparation

Dr. Irtiqa Mohammad: literature search, manuscript preparation and statistical analysis

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Conflict of Interest

Not available

Financial Support

Not available

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