ECRONICON OPEN ACCESS

EC NEUROLOGY
Research Article

Association between Ocular Abnormalities, Duration of Stroke and Risk Factors of Stroke among Stroke Patients in University of Calabar Teaching Hospital, Nigeria

Kennedy U Nwachukwu[1], Affiong A Ibanga[1], Bassey A Etim[1] and Ekanem Philip-Ephraim[2]*

[1]*Department of Ophthalmology, University of Calabar Teaching Hospital, Calabar, Nigeria*

[2]*Department of Internal Medicine, University of Calabar Teaching Hospital, Calabar, Nigeria*

***Corresponding Author:** Ekanem Philip-Ephraim, Department of Internal Medicine, University of Calabar Teaching Hospital, Calabar, Nigeria.

Received: May 20, 2019; **Published:** July 12, 2019

Abstract

Background and Methodology: The study was done to determine a possible association between ocular abnormalities, duration of Stroke and common risk factors of Stroke in patients diagnosed with Stroke in University of Calabar Teaching Hospital. This was a hospital based observational study where all consecutive stroke patients, both old and new cases who met inclusion criteria were examined in details for ocular abnormalities. Patients' medical records were searched to obtain information about status on hypertension, diabetes mellitus, and hyperlipidemia. All information obtained from medical records were confirmed by the patient or care-giver. Duration of Stroke was the time since the stroke event (or the first event, for those with more than occurrence). Data were collected and analyzed with SPSS 20. Inferential statistics (Pearson chi-square and Fisher's exact tests) were used to test the significance between variables. Binary logistic regression was done to check for strength of association between ocular abnormalities and risk factors of stroke. A confidence level of 95% was adopted, and p-value of less than 0.05 was considered statistically significant.

Results: A total of 760 eyes of 380 patients were examined. The mean age was 59.5 years ± 11.1 with age range 18 to 87 years. There were 197 males (51.8%) and 183 (48.2%) females. The most common ocular abnormalities were hypertensive retinopathy (30%), lens opacities (29.7%), ocular surface disorder (17.1%), facial nerve palsy (15.5%) and glaucoma (15.5%). The frequency of hypertensive retinopathy, facial nerve palsy and disorders of ocular motility decreased with increasing duration from the onset of stroke (p-values: 0.001, < 0.0001 and 0.002 respectively), while glaucoma frequency increased with increasing duration from the onset of stroke (p-value: 0.005). Retinal arteriosclerosis was less frequent in subjects with diabetes mellitus (p-value: 0.015). Diabetic retinopathy was more frequent in those with hyperlipidemia (p-value: 0.006).

Conclusion: The neuro-ophthalmic ocular abnormalities (except for optic neuropathies) reduce with increasing duration from the onset of stroke. Retinal artery occlusion was seen only in hypertensive subjects but the statistical evidence was not strong enough. Most of the ocular abnormalities increase in frequency in age as would be expected. The risk factors of stroke have specific ocular manifestations which form a majority of the ocular abnormalities seen in stroke.

Keywords: *Ocular Abnormalities; Stroke; Stroke Duration; Hypertension; Diabetes Mellitus; Dyslipidemia; Calabar; Nigeria*

Introduction

Stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" [1]. It is also referred to as Acute Brain Insult.

Recent researches suggest a new definition which will not have a time criterion but rather will be based on tissue damage [2]. However, Stroke is a clinical diagnosis and the above definition remains acceptable by World Health Organization (WHO).

The eye and the brain share several features in common especially as both develop from the diencephalon. It has been suggested that about 30% of neurons in the cerebral cortex are devoted to vision [3]. These close associations therefore suggest that pathology of the brain will affect the eye more than any other organ and ocular features of Stroke may be more common than previously acknowledged.

The major risk factors of Stroke are hypertension, diabetes mellitus, and dyslipidaemia. These risk factors are also known to affect the eye in different ways. The ocular abnormalities seen in Stroke patients can be from the stroke sequelae or tell-tale signs of underlying risk factors. This study seeks to explore the relationship between these risk factors, the duration from the onset of Stroke and ocular abnormalities.

Methods

This study was a hospital based observational cross-sectional clinical study. All old and newly diagnosed Stroke patients who were 18 years and older and managed by the Neurology Unit, Department of Internal Medicine, University of Calabar Teaching Hospital (UCTH) were eligible for recruitment into the study after their consent. Old Stroke patients were recruited from clinic visits while new patients were recruited from the clinic, the accident and emergency unit and from the medical wards. The recruitment was done from January to October 2016. Non-probability serial recruitment method was used. Subjects were identified with both their serial numbers and hospital numbers. Their hospital folders were marked to avoid being included more than once in the study. Approval for the study was given by the Health Research Ethics Committee of UCTH. Both written and verbal informed consents were obtained from the subjects by the Principal Investigator.

Blood pressure recordings, fasting lipid profile and fasting blood sugar results were extracted from subjects' folders by the Principal Investigator. Old Stroke patients who were known diabetics or hypertensives were recorded as such regardless of their current blood sugar level and blood pressure measurements respectively. New Stroke patients were classified into diabetic or hypertension groups based on the clinical diagnosis of the physicians. Other information obtained from the subjects or care-giver included the duration of stroke, past medical history, major ocular complaints and pre-morbid ocular conditions. General detailed ocular examination was done either in the clinic or in the wards by the Principal Investigator. Examination protocol sheet was used for uniformity and completeness.

Distance visual acuity (VA) was measured using either the Snellen's or E-chart, while near VA was measured with a Near-Vision test card. Visual acuity was done with a pin-hole when presenting visual acuity was 6/18 or worse. However, visual acuity test with pin-hole was done for subjects who could understand the instructions. The World Health Organization classifies visual acuity measurements into normal/mild visual impairment, moderate visual impairment, severe visual impairment and blindness. For the purpose of presenting results for this study, 'normal' and 'mild' were separated to highlight those who may need some intervention.

Confrontational visual field assessment was carried out from a distance of one metre. Subjects were examined for facial asymmetry especially from facial nerve palsy. The eyelids were evaluated for ptosis by using the Margin-Reflex-Distance (MRD-1). Skew deviation and ocular mal-alignment was looked out for using the Hirschberg test. Ocular motility tests were done by moving a finger in the diagnostic positions of gaze. Vergence and duction tests were done to check for gaze palsies and cranial nerve palsies.

The ocular surface and anterior segment were examined with a bright penlight for ocular surface irregularities and corneal clarity. The anterior chamber depth was assessed using the eclipse sign and pupillary light reflexes also assessed. The intraocular pressure was checked with a Perkins handheld tonometer. The Perkins tonometer head was disinfected with 75% methylated spirit swabs and wiped with normal saline swab between patients.

The subjects' pupils were dilated with Trophen eye drops (ARISTOPHARMA LTD; batch No. 15J06), a combination of 5% phenylephrine and 0.8% tropicamide prior to fundoscopy. This was done by a nurse. One drop was instilled into each eye and the subject asked to close the eyes to reduce systemic absorption. Most of the subjects' pupils were adequately dilated in 10 - 15 minutes after only one drop. Some patients needed a second instillation.

A dilated direct fundoscopy (with Keeler Professional ophthalmoscope) was done on all subjects. Media opacities especially from lens opacities were assessed by observing the red reflex with the ophthalmoscope dialed to +10 dioptre, from a distance of about one foot. The optic disc was assessed for signs of neuropathy and disc edema. The retina was studied in quadrants, following the vascular arcades, looking out for retinal haemorrhages, cotton wool spots, focal retinal narrowing, arteriovenous nipping and any other lesion. Further examinations were carried out according to individual needs and for the purpose of management.

Data analysis

Data from the ocular evaluation form were inputted into statistical package for social sciences (SPSS) software for Windows version 20 (SPSS inc., Chicago, IL, USA) and analyzed using same. Descriptive statistics (frequencies, percentages, means and standard deviation)

were used to summarize the variables. Pearson chi-square and Fisher's exact tests were used to test the significance between variables. Binary logistic regression was done to check for strength of association between ocular abnormalities and risk factors of stroke. A confidence level of 95% was adopted, and p-value of less than 0.05 was considered statistically significant.

Results

A total of 760 eyes of 380 stroke patients were examined. The mean age of the subjects was 59.5 years ± 11.1 and age range 18 to 87 years. There were 197 males (51.8%) and 183 females (48.2%). The mean age was 60.2 ± 11.1 for males and 58.7 ± 11.1 for females. There was no statistical difference between the two, t(378) = 1.352, p-value = 0.177.

Tables 1 and 2 show the different ocular abnormalities recorded in the subjects.

Ocular Abnormalities Anterior Segment	Frequency (%)	Ocular Abnormalities Posterior Segment	Frequency (%)
Mild to moderate lens opacities	113 (29.7)	Hypertensive Retinopathy	115 (30.3)
Ocular surface disorder	65 (17.1)	Glaucoma	55 (14.5)
Facial nerve palsy	59 (15.5)	Diabetic retinopathy	50 (13.2)
Refractive error	51 (13.4)	Age Related Maculopathy	43 (11.3)
Disorders of ocular motility	46 (12.1)	Retinal arteriosclerosis	33 (8.7)
Dense cataract	20 (5.3)	Disc edema/papilloedema	32 (8.4)
Ptosis	17 (4.5)	Other retinopathy/detachment	29 (7.6)
Third nerve/Sixth nerve palsy	7 (1.8)	Retinal vein occlusion	26 (6.8)
Lid retraction	4 (1.1)	Other optic neuropathy	19 (5.0)
		Retinal artery occlusion/embolus	10 (2.6)
		Vitreous hemorrhage/opacities	6 (1.6)
		Other maculopathy	6 (1.6)

Table 1: *Ocular abnormalities in Stroke patients in UCTH.*

Other retinopathy refers to retinitis pigmentosa, exudative and pigmentary retinopathies of uncertain aetiology.

Other optic neuropathy refers to optic atrophy and neuropathy other than glaucomatous.

Neuro-Ophthalmic Abnormality	Frequency (%)
Facial nerve palsy	59 (15.5)
Disorders of ocular motility	46 (12.1)
Cortical visual impairment	21 (5.5)
Ptosis	17 (4.5)
Homonymous hemianopia	14 (3.7)
Third nerve/sixth nerve palsy	7 (1.8)
Lid retraction	4 (1.1)

Table 2: *Neuro-ophthalmic abnormalities in Stroke subjects in UCTH.*

Relationship between ocular abnormalities and risk factors of stroke

The relationships between ocular abnormalities and three risk factors of stroke (hypertension, diabetes and hyperlidaemia) were analyzed (Table 3).

Ocular abnormalities	Hypertensive		Statistical values	
	No Freq. (%)	Yes Freq. (%)	Chi-square	p-value
Hypertensive retinopathy	9 (10.1%)	106 (36.4%)	22.361	< 0.001
Facial Nerve Palsy	15 (16.9%)	44 (15.1%)	0.156	0.693
Disorders of ocular motility	6 (6.7%)	40 (13.7%)	3.142	0.076
Cortical visual impairment	6 (6.7%)	15 (5.2%)	0.329	0.566
Diabetic retinopathy	13 (14.6%)	37 (12.7%)	0.214	0.644
Glaucoma	8 (9.0%)	47 (16.2%)	2.825	0.093
Other optic neuropathy	6 (6.7%)	13 (4.5%)	0.742	0.389
Other retinopathies	7 (7.9%)	18 (6.2%)	0.313	0.576
Retinal arteriosclerosis	9 (10.1%)	24 (8.2%)	0.299	0.585
Retinal artery occlusion	0 (0.0%)	10 (3.4%)	3.141	0.076
Retinal vein occlusion	5 (5.6%)	21 (7.2%)	0.273	0.601

Table 3: *Relationship between ocular abnormalities and hypertension among Stroke patients in UCTH.*

Hypertension: Ocular abnormalities were more common in hypertensive subjects than in non-hypertensives but the relationships were not statistically significant, except for hypertensive retinopathy. All the ten patients who had features of retinal artery occlusion were known hypertensives but the sample size was not powered enough to confirm a strong association between retinal artery occlusion and hypertension.

Diabetes mellitus: There was a statistically significant relationship between diabetes mellitus and three ocular abnormalities; (diabetic retinopathy, retinal arteriosclerosis and other retinopathies). Other retinopathies here refer to pigmentary retinopathies and exudative retinopathies of uncertain aetiology.

Diabetic retinopathy was obviously seen only in subjects who had diabetes mellitus (p-value: < 0.0001), but the frequency of retinal arteriosclerosis and other retinopathies were decreased in subjects who have diabetes mellitus (Table 4).

Ocular abnormalities	Diabetes mellitus		Statistical values	
	No Freq. (%)	Yes Freq. (%)	Chi-square	p-value
Hypertensive retinopathy	83 (30.0%)	32 (31.1%)	0.043	0.835
Facial Nerve Palsy	44 (15.9%)	15 (14.6%)	0.100	0.752
Disorders of ocular motility	37 (13.4%)	9 (8.7%)	1.506	0.220
Cortical visual impairment	15 (5.4%)	6 (5.8%)	0.024	0.876
Diabetic retinopathy	4 (1.4%)	46 (44.7%)	122.718	< 0.0001
Glaucoma	46 (16.6%)	9 (8.7%)	3.755	0.053
Other optic neuropathy	15 (5.4%)	4 (3.9%)	0.371	0.543
Other retinopathies	23 (8.3%)	2 (1.9%)	4.944	0.026
Retinal arteriosclerosis	30 (10.8%)	3 (2.9%)	5.935	0.015
Retinal artery occlusion	9 (3.2%)	1 (1.0%)	1.521	0.217
Retinal vein occlusion	17 (6.1%)	9 (8.7%)	0.797	0.372

Table 4: *Relationship between ocular abnormalities and diabetes mellitus among Stroke patients in UCTH.*

Hyperlipidemia: With the exception of diabetic retinopathy, no other ocular abnormality showed a statistically significant relationship with lipid status (Table 5). There were 207 (54.5%) subjects whose fasting lipid results were not available because the test was not done or results were missing. Among the subjects with available fasting lipid profile, diabetic retinopathy was seen to be more frequent in those with hyperlipidemia. A significantly higher percentage of subjects with high lipid status (32%) had diabetic retinopathy compared to 14.9% diabetic retinopathy among those with normal lipid status (p-value: 0.006).

Ocular abnormalities	Lipid status		Statistical values	
	Within normal Freq. (%)	High Freq. (%)	Chi-square	p-value
Hypertensive retinopathy	51 (34.5%)	5 (20.0%)	2.787	0.248
Facial Nerve Palsy	30 (20.3%)	1 (4.0%)	5.703	0.058
Disorders of ocular motility	18 (12.2%)	1 (4.0%)	1.715	0.424
Cortical visual impairment	6 (4.1%)	2 (8.0%)	1.113	0.568
Diabetic retinopathy	22 (14.9%)	8 (32.0%)	10.359	0.006
Glaucoma	15 (10.1%)	3 (12.0%)	4.308	0.116
Other optic neuropathy	6 (4.1%)	1 (4.0%)	0.608	0.738
Other retinopathies	11 (7.4%)	3 (12.0%)	1.910	0.385
Retinal arteriosclerosis	13 (8.8%)	2 (8.0%)	0.017	0.992
Retinal artery occlusion	7 (4.7%)	1 (4.0%)	5.405*	0.062*
Retinal vein occlusion	7 (4.7%)	2(8.0%)	1.699	0.428

Table 5: *Relationship between ocular abnormalities and lipid status among stroke patients in UCTH.*
**Fisher's exact test used since there were more than 1 cell with < 5 expected counts.*

Most common retinal abnormality

Hypertensive Retinopathy: This was the most common retinal abnormality, and thus further analysis was done. There were 291 hypertensive subjects, 106 (36.4%) of them showed features of hypertensive retinopathy, but 9 (10.1%) among non-hypertensive subjects who never had recorded increases in blood pressure also showed features suggestive of hypertensive retinopathy. Thus, hypertensive retinopathy is more prevalent in known hypertensives.

A logistic regression was performed to ascertain the contribution of age, sex, diabetes mellitus and hyperlipidemia on the development of hypertensive retinopathy. Age, diabetes mellitus and hyperlipidaemia did not show significant effects on development of hypertensive retinopathy as shown in table 6. Females were 1.5 times more likely to have hypertensive retinopathy but this did not show a strong statistical significance (OR = 1.54; CI: 0.972 - 2.427; p = 0.055).

Relationship between duration from time of the onset of stroke and ocular abnormalities

The frequency of facial nerve palsy reduced with increasing duration from time of the onset of Stroke (p-value: < 0.0001), while frequency of glaucoma increased with increasing duration from time of the onset of Stroke, (p-value: 0.005). The reducing frequency for disorders of ocular motility with Stroke duration was also found to be significant (p-value: 0.002), but the reduction was not stepwise because of insufficient cell numbers size (only 1 subject) in the "3 - 12 months" group. Hypertensive retinopathy was seen more in the group of subjects who were examined within 3 months of the onset of stroke. The frequency of hypertensive retinopathy was seen to reduce with increasing duration from time of the onset of stroke.

Independent variables	Hypertensive Retinopathy		Odds ratio	Confidence Interval
	Yes	No		
Age Groups				
≤ 40 years	7 (50%)	7 (50%)	0.991	0.971 - 1.02
41 to 60 years	63 (30.3%)	145 (69.7%)		
> 60 years	45 (28.5%)	113 (71.5%)		
Sex				
Male	51 (25.9%)	146 (74.1%)	1.536	0.972 - 2.427
Female	64 (35%)	119 (65%)		
Diabetes mellitus	32 (31.1%)	71 (68.9%)	1.038	0.618 - 1.744
Hyperlipidaemia	5 (20%)	20 (80%)	0.981	0.679 - 1.417

Table 6 : *Effects of age, sex, diabetes and hyperlipidaemia on hypertensive Retinopathy.*

Ocular abnormalities	Duration of time from stroke onset			Statistical values	
	< 3 months Freq. (%)	3 - 12 months Freq. (%)	> 1year Freq. (%)	Chi-square	p-value
Facial Nerve Palsy	46 (28.2%)	7 (13.2%)	6 (3.7%)	37.856	< 0.0001
Hypertensive retinopathy	66 (40.5)	13 (24.5)	36 (22.0)	14.274	0.001
Disorders of ocular motility	30 (18.4%)	1 (1.9%)	15 (9.1%)	12.630	0.002
Cortical visual impairment	12 (7.4%)	3 (5.7%)	6 (3.7%)	2.150	0.341
Diabetic retinopathy	21 (12.9%)	7 (13.2%)	22 (13.4%)	0.20	0.990
Glaucoma	13 (8.0%)	8 (15.1%)	34 (20.7%)	10.765	0.005
Other optic neuropathy	5 (3.1%)	2 (3.8%)	12 (7.3%)	3.303	0.192
Other retinopathies	10 (6.1%)	3 (5.7%)	12 (7.3%)	0.270	0.874
Retinal arteriosclerosis	13 (8%)	3 (5.7%)	17 (10.4%)	1.299	0.522
Retinal artery occlusion	3 (1.8%)	1 (1.9%)	6 (3.7%)	1.047*	0.745*
Retinal vein occlusion	13 (8.0%)	4 (7.5%)	9 (5.5%)	0.842	0.652

Table 7 : *Relationship between duration of stroke and ocular abnormalities among stroke patients in UCTH.*
**Obtained by Fisher's exact test since there was more than 1 cell with < 5 cells.*

Discussion

Some risk factors of Stroke are associated with some known ocular manifestations. The ocular abnormalities seen in index subjects were more associated with risk factors of Stroke than the Stroke pathology itself. Hypertensive retinopathy and diabetic retinopathy were undoubtedly caused by systemic hypertension and diabetes mellitus respectively. Although some of the subjects who never had recorded elevated blood pressure showed features of hypertensive retinopathy, it may be argued that they may have had some unidentified episodes of significantly elevated blood pressure. Other risk factors did not have any effect on frequency of hypertensive retinopathy and diabetic retinopathy. All the subjects who were seen to have retinal artery occlusions were known hypertensives. It is well documented in literature that systemic hypertension is one of the major risk factors to branch retinal artery occlusions [4].

Diabetic retinopathy was found to be more prevalent in subjects who had hyperlipidaemia. There have been several conflicting results regarding the relationship between dyslipidaemia and diabetic retinopathy. While a majority of these studies [5,6] found worsening of diabetic retinopathy with high serum lipids, fewer studies found no significant relationship between diabetic retinopathy and serum lipids [7]. However, based on the relationships between protein kinase C, advanced glycation end products and lipids in the pathogenesis of dia-

betic retinopathy [8], hyperlipidaemia is more likely to increase the prevalence of diabetic retinopathy or even accelerate its progression in Stroke patients.

The index study found a significant relationship between retinal arteriosclerosis and diabetes mellitus. The prevalence of retinal arteriosclerosis and other retinopathies were reduced in subjects who had diabetes mellitus. This finding agrees with the Multi-Ethnic Study of Arteriosclerosis (MESA) carried out in the United States. MESA reported significant increase in retinal arteriolar and venular caliber in the presence of diabetes mellitus [9]. Narrowing of retinal arterioles (which is seen in retinal arteriosclerosis) is not a typical feature of diabetes mellitus. Diabetes causes loss of pericytes of endothelial cells seen as microaneurysms, so this tendency to widening of vessel calibre will dominate over any vascular narrowing and reduce the likelihood of arteriosclerosis in diabetes mellitus.

Lens opacities were associated with increasing age only. There was no significant effect of hypertension, diabetes or hyperlipidemia on the frequency of lens opacities.

The percentage of subjects with glaucoma was seen to increase with increasing duration of Stroke. It is likely that most of the subjects (76.6%) were hypertensive and hypertension (the most common risk factor for stroke) is also associated with risk of glaucoma development and progression [10]. Glaucoma being a progressive disease was also worsened by vascular autoregulatory insufficiency which is implicated in many Stroke cases. Different studies have found an association between glaucoma and Stroke. One study has shown that dynamic cerebral auto-regulation is impaired in patients with glaucoma [11]. Another study done in Taiwan showed that patients with glaucoma have a significantly higher risk of developing Stroke than those without glaucoma [12]. These studies suggest that impaired vascular auto-regulation is the common risk factor between Stroke incidence and glaucoma progression. A similar increasing frequency with duration from Stroke onset was also noticed with 'other optic neuropathies'.

The frequency of hypertensive retinopathy was seen to reduce with increasing duration from time of Stroke onset. That is, those whose Stroke event had occurred more than 3 months before the time of study had fewer findings suggestive of hypertensive retinopathy. This reduction is likely because some signs of hypertensive retinopathy like cotton wool spots and flame-shaped haemorrhages are transient and may not be seen in subjects who may have controlled their blood pressure over time.

The frequency of facial nerve palsy reduced with increasing duration from the time of the onset of Stroke, simply because the nerve impulse improves with time as it gradually recovers from ischaemic insult. The frequency of disorders of ocular motility also reduced with increasing duration from the time of onset of Stroke. Disorders of ocular motility in Stroke result from disruption of supra-nuclear control pathways in brain. However, infranuclear pathways exist which can take over control of some ocular motility [13]. Also, the nuclei in different gaze centers which control ocular movements often recover from ischemic insults with improvement of motility disorders [14].

Conclusion

He neuro-ophthalmic ocular abnormalities (except for optic neuropathies) reduce with increasing duration from the onset of Stroke. Retinal artery occlusion was seen only in hypertensive subjects but the statistical evidence was not strong enough. Most of the ocular abnormalities increase in frequency with age as would be expected. The risk factors of stroke (age, hypertension, diabetes, hyperlipidaemia) have specific ocular manifestations which form a majority of the ocular abnormalities seen in Stroke.

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Volume 11 Issue 8 August 2019