ORIGINAL ARTICLE

Risk Factors Associated with Second and Subsequent Strokes in an Adult Stroke Population in a Rural Community in South-East Nigeria

Kelechi O **ENWEREJI**[1], Maduaburochukwu C **NWOSU**[1], Adesola **OGUNNIYI**[2], Paul O **NWANI**[1], Azuoma L **ASOMUGHA**[1], Ezinna E **ENWEREJI**[3]

AFFILIATIONS
[1]Neurology Unit, Dept of Medicine, Nnamdi Azikiwe University Teaching Hospital Nnewi, Anambra State NIGERIA
[2]Neurology Unit, Dept of Medicine, University College Hospital Ibadan Oyo State NIGERIA
[3]Dept of Community Medicine / Nursing Sciences, College of Medicine, Abia State University, Uturu, Abia State NIGERIA

CORRESPONDING AUTHOR
Kelechi O **ENWEREJI**
Neurology Unit, Department of Medicine, Nnamdi Azikiwe University Teaching Hospital Nnewi, Anambra State NIGERIA

Email: doublekay2001@yahoo.com
Phone: +234 803 386 1317

DISCLOSURES:
No disclosures.

Received: 30th May, 2017
Accepted: 29th June, 2017

ABSTRACT
Background: Stroke, and by extrapolation, recurrent stroke is estimated to constitute an enormous burden in Sub-Saharan Africa. This is believed to stem from the ever increasing burden of the risk factors for stroke in our population.
Objective: To determine the specific risk factors for stroke and recurrent stroke in an adult stroke population in a rural community in South-East, Nigeria.
Methodology: We carried out a case-controlled analytical cross sectional study on an adult stroke population screened out from a predominantly low-income community in South-East Nigeria. We used a pre-tested Risk Factor for Stroke/Recurrent Stroke Questionnaire, focused clinical examination and collected blood samples for laboratory investigations.
Results: We identified 10 stroke subjects out of which 3 had recurrent stroke. Furthermore, 10 age- and sex-matched controls were randomly selected from the stroke negative population. All the stroke subjects were hypertensive in contradistinction to the controls (10 subjects vs 2 controls respectively, $p=0.001$). The association between the other risk factors (diabetes mellitus and tobacco use) and the number of stroke risk factors present in an individual was less significant for stroke than for recurrent stroke.
Conclusion: Hypertension was identified as the most frequent risk factor associated with stroke and recurrent stroke, in the study. This is comparable with other local and international studies.

Keywords: *Africa, developing country, population screening, recurrent stroke, risk variables*

INTRODUCTION

The burden of stroke with its attendant disability alongside other non-communicable and communicable diseases in Sub-Saharan African communities is enormous. Recurrent stroke is said to occur when an individual experiences a second and/or subsequent stroke episodes. Traditionally, a previous stroke is an established risk factor for a subsequent stroke. However, recurrent stroke is not observed in every patient with a previous stroke. This presupposes that there

are some permissive factors which, if present in an individual with previous stroke, might particularly predispose that individual to recurrent strokes. These factors when discovered would enable health care providers formulate health policies that may tackle some of the highlighted risk factors and probably reduce the burden of recurrent stroke. This will, in turn, save the country huge economic losses from long-term disability and death.

This study aimed at determining the specific risk factors for stroke and recurrent stroke in an adult stroke population in a rural community in South-East Nigeria.

METHODOLOGY

This was a case-controlled analytical cross-sectional study conducted in the Neuroepidemiology Out-patient Clinic of Comprehensive Health Centre Ukpo, an outpost of Nnamdi Azikiwe University Teaching Hospital Nnewi, Anambra State, Nigeria. It is the only Comprehensive Health Centre in Ukpo; the headquarters of Dunukofia Local Government Area in Anambra State, South-East Zone of Nigeria. It is a predominantly low-income rural and agrarian community with a population of 17,840 (*Based on data from The National Population Commission of Nigeria*). Majority of the residents of the community are Christians, indigenous and of the Igbo ethnic group.

Ethical clearance was obtained from the Ethical Committee of the Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, prior to the commencement of the study and each participant gave an informed consent.

The study was conducted after a community survey which was used to screen out all adult stroke patients from the community. It was conducted in the Out-patient Clinic of the NAUTH Health Centre in Ukpo using pre-tested semi-structured risk factors for stroke/recurrent stroke questionnaires, focused clinical examination and collection of samples for laboratory investigations. A total of 10 stroke subjects out of which 3 had recurrent stroke, participated in the study. An equal number (10) of stroke-negative controls were randomly selected from those who screened negative for stroke to match subjects by age and sex. These controls were screened and examined for risk factors as was done for the stroke subjects. The diagnosis of stroke was clinical, based on the WHO definition.

Procedure

Physical Examination: The radial pulse was palpated to check for irregularity, asymmetry and thickened wall. The other peripheral pulses were also palpated for symmetry. The blood pressure of each participant was measured in the arm using a standard adult arm cuff with Accouson mercury-type sphygmomanometer. The average of the two readings was taken as the blood pressure. The praecordium of each participant was palpated for apical heave and auscultated for abnormal heart sounds and murmurs. The carotid areas were also auscultated for bruits.

Each participant was assessed for deviation of the mouth or any residual weakness of the face. Muscle power and tone were assessed in the limbs for residual weakness. The deep tendons of the biceps, triceps, patellar and Achilles' were struck with a tendon hammer for residual exaggerated reflexes. Furthermore, the plantar reflexes were assessed for residual extensor response.

Laboratory Evaluation: Blood samples were taken for laboratory investigations from participants on their second visit because of the requirement for fasting. Participants were instructed to carry out a 9 to12-hour overnight fast on their first visit. The fasting blood glucose was estimated using the glucose oxidase method as described by Trinder while the serum triglycerides, total cholesterol and High Density Lipoprotein (HDL) cholesterol were determined by the enzymatic colorimetric method as described by Searcy, Allain, *et al* and Burstein and Mortin, respectively.[1,2,3,4]

The Low Density Lipoprotein (LDL) cholesterol was then determined

mathematically using the Friedewald formula as follows (all values are in mmol/l):

LDL cholesterol = Total cholesterol – HDL cholesterol – (Triglycerides ÷ 2.17).[5]

Definition of Terms

Stroke: The diagnosis of stroke was clinical, based on the WHO definition and classification into ischaemic or haemorrhagic types was done using the Siriraj Stroke Score. Computed Tomography (CT) scan using the Hispeed Helical/Spiral Scanner by General Electronics America was done when classification was indeterminate. Stroke was defined as a sudden onset focal or global neurological deficit lasting more than 24 hours or leading to death; of no other cause other than vascular.

***First-ever stroke*:** First episode of stroke.

***Recurrent stroke*:** Second and subsequent stroke episodes after the first-ever stroke.

***Diabetes mellitus*:** A history of previously diagnosed diabetes mellitus; use of oral hypoglycaemics or insulin; or, fasting blood glucose of ≥ 7.0mmol/l (126 mg/dl).

***Hypertension*:** A history of previously diagnosed hypertension; use of antihypertensives or elevated blood pressure of ≥140mmHg systolic; or ≥90mmHg diastolic; or clinical signs of sustained systemic high blood pressure like a heaving apex, loud aortic component of the second heart sound and left ventricular hypertrophy.

***Dyslipidaemia*:** A history of previously diagnosed dyslipidaemia; use of lipid lowering drugs or fasting triglycerides ≥1.7mmol/l (150mg/dl), fasting total cholesterol ≥5.1mmol/l (200mg/dl); fasting low density lipoprotein (LDL) cholesterol ≥2.6mmol/l (100mg/dl) or fasting high density lipoprotein (HDL) cholesterol ≤1.0mmol/l (40mg/dl).

Benefits/Hazards to Participants: Participants were availed of the results of the tests and examinations carried out on them at no cost to them. Those who were found to have some risk factors like hypertension were advised on the need to access medical care and followed up at the out-patient community neurology service. The hazards were limited to the complications of venepuncture which were minimized by strictly observing precautionary measures for venepuncture.

Data Collection and Analysis: The data were carefully collected, confidentially recorded and analyzed. Study code was used. The data collected were analyzed using the *Epi Info* 3.5.1 2008, statistical software. The descriptive study was analyzed to determine the point prevalence (crude prevalence on prevalence day), age-adjusted prevalence and the age and sex-specific prevalence, while the analytical study determined the relative risk of recurrent stroke. Continuous variables were presented as means with standard deviation while categorical variables were presented as proportions. Chi-square was used to compare the qualitative risk variables of the groups i.e. the controls, stroke patients and recurrent stroke patients, while Z-score was calculated to compare any two quantitative variables. The Fisher's Exact Test was used to compare qualitative risk variables and 2-sample t-test for the means of the risk variables owing to small sample size. Analysis of variance (ANOVA) was done to compare the risk factors in the three groups of patients. Correlation of continuous risk variables was done using Pearson correlation coefficient.

RESULTS

Demography of the Study Population

Overall, 20 persons were recruited for the study comprising 10 subjects and 10 controls that were matched for age and sex. A total of 10 (100%) persons had stroke out of which 3 (30%) had recurrent stroke. Overall, those with stroke had a male to female ratio of 3:2 while those with recurrent stroke had a ratio of 2:1. The mean age for stroke was 60.7 ± 11.4 years with range of 47-86years while the mean age for recurrent stroke was 59.7 ± 4.7 years with a range of 56-65years.

Clinical Risk Variables between all Stroke / Recurrent Stroke Subjects and Controls

The various identifiable stroke risk factors in all stroke subjects and controls were compared (*Table 1*). It also compared the risk

factors in the recurrent stroke subjects with that of the controls. Hypertension was the most frequent identifiable stroke risk factor among stroke subjects (both first-ever and recurrent) and controls, having a frequency of 10 (100%) and 3 (30%), respectively. Worthy of note is that 4 (40%) of the stroke subjects had >1 identifiable stroke risk factor by medical history while none of the controls had >1 identifiable risk factor for stroke. Hypertension was the only identifiable stroke risk factor between the two groups that achieved a statistically significant difference (*p=0.001*) when the Fisher's Exact test was applied.

Table 1. Comparison of the clinical variables between all stroke/recurrent stroke subjects and controls

Risk factors	**All Stroke No.(%) n=10**	**Control No.(%) n=10**	**p-value**
Hypertension	10 (100)	2 (20)	p = 0.001*
Diabetes mellitus	3 (30)	0 (0)	p = 0.211
Tobacco	2 (20)	0 (0)	p = 0.474
No. of risk factors			p = 0.087
≤1	6 (60)	10 (100)	
>1	4 (40)	0 (0)	

Risk factors	Recurrent Stroke No.(%) n=3	Control No.(%) n=10	p-value
Hypertension	3 (100)	2 (20)	p = 0.035* RR = 1.5
Diabetes mellitus	2 (66.7)	0 (0)	p = 0.038*
Tobacco	2 (66.7)	0 (0)	p = 0.038*
No. of risk factors			P = 0.003*
≤1	0 (0)	10 (100)	
>1	3 (100)	0 (0)	

*Significant

All the identifiable stroke risk variables achieved statistical significance (*p<0.05*) when only the recurrent stroke subjects were compared with controls using the Fisher's exact test. All of the recurrent stroke subjects had a multiplicity of identifiable risk factors of more than 3 unlike the controls.

Lipid Profile / Fasting Blood Sugar (FBS) of all Stroke Subjects and Controls

The laboratory results (lipid profile and fasting blood sugar) between all strokes (recurrent and first ever) and controls with their t-test and p-values were compared for differences. All but the serum triglycerides, serum HDL and HDL:LDL ratio showed a statistically significant difference at p<0.05 as shown below (*Table 2*).

Table 2. Lipid profile and FBS compared between all strokes and controls

Parameters	**All Strokes (n=10)**	**Controls (n=10)**	**t-test**	**p-value**
Mean Serum LDL(mmol/l)	2.17	2.13	0.109	0.915
Mean Serum Triglyceride (mmol/l)	1.78	1.15	3.620	0.002*
Mean Serum HDL (mmol/l)	2.03	1.39	2.878	0.010*
Mean Serum HDL/LDL ratio	1.17	0.67	2.987	0.008*
Mean Fasting blood sugar (mmol/l)	6.28	4.75	1.052	0.307

*Significant

Table 3. Mean of lipid profile and FBS compared between recurrent strokes and controls

Parameters	**Recurrent Strokes (n=3)**	**Controls (n=10)**	**t-test**	**p-value**
Mean Serum LDL(mmol/l)	0.95	2.13	-12.070	0.000*
Mean Serum Triglyceride (mmol/l)	2.32	1.15	4.936	0.026*
Mean Serum HDL (mmol/l)	1.32	1.39	-0.860	0.428
Mean Serum HDL/LDL	1.40	0.67	11.220	0.001*
Mean Fasting blood sugar (mmol/l)	10.80	4.75	3.032	0.110

*Significant

Lipid profile and FBS between Recurrent Strokes Subjects and Controls

The means of the laboratory results screening for stroke risk factors between recurrent stroke subjects and controls were compared in *Table 3*. However, only the means of serum LDL, serum triglycerides and serum HDL/LDL showed a statistically significant difference between the two groups at $p=<0.05$.

DISCUSSION

Hypertension

Hypertension is traditionally known to be the most prevalent risk factor for stroke. Similarly, several studies in both the developed and developing countries support this fact.[6,7,8,9,10,11,12] The risk for stroke has been found to increase linearly with a rise in both systolic and diastolic blood pressure.[13,14] Conversely, optimal control of blood pressure has been established to reduce the risk of stroke.[11] This was replicated in the results of this study as virtually all the stroke and recurrent stroke subjects (100%) were hypertensives while 20% of the controls were reported being hypertensive. This is comparable to about 90% prevalence found among subjects in Nigerian studies.[11] Owolabi, *et al*, reported a similar prevalence of 99% among stroke patients in Ibadan.[15]

However, Osuntokun, *et al*, had earlier reported a prevalence of 80% among stroke patients in the Ibadan Stroke Registry using a higher blood pressure reading cut off of 160/100 mmHg.[16] Similarly, Bwala reported a prevalence of 79% in a hospital based study in Maiduguri Northern Nigeria, using a cut off of 160/95 mmHg.[17] In one study in Harare Kenya, high blood pressure was the single most important preventable risk factor for stroke with a prevalence of 93% in haemorrhagic stroke and 53% in ischaemic stroke.[18]

Diabetes Mellitus and Serum Lipids

Diabetes mellitus is one of the most common modifiable risk factors for stroke.[11,19] Other identifiable risk factors which were found to be significantly more prevalent in the stroke or recurrent stroke subjects than controls include diabetes mellitus, tobacco use and the presence of more than one risk factor ($p<0.05$). This is in agreement with the results of several studies in Nigeria that reported diabetes mellitus as an important risk factor for stroke in association with the other risk factors like hypertension, excessive alcohol consumption, previous or family history of stroke, advancing age and tobacco use.[11,17,20,21,22,23]

In the United States, Lai, *et al*, found that apart from hypertension, the presence of multiple of risk factors (like tobacco smoking, excessive alcohol use and diabetes mellitus) in a patient were the most important risk factors for ischaemic stroke recurrence.[24] In Pakistan, Khan, *et al*, found that one of the most common risk factors for stroke was diabetes mellitus (36.3%).[25] However, the mean fasting blood sugar found in the survey was not significantly higher in the stroke or recurrent stroke subjects than in the controls when compared separately ($p=0.307$ *and* $p=0.110$, respectively).

Serum lipids have been found to be an important risk factor for stroke in western countries.[26] Furthermore, serum triglycerides have particularly been found to be an independent risk factor for stroke.[27] The mean serum triglycerides level in this study was found to be significantly higher among stroke or recurrent stoke subjects than controls ($p=0.002$ and $p=0.026$, respectively). Ogunrin, *et al,* also, reported that elevated serum triglycerides was strongly associated with first ever stroke in Benin, Southern Nigeria.[61] However, this is in contradistinction to earlier studies that found poor relationship between serum lipids and stroke.[62,63] Also, there was a significantly higher mean HDL:LDL ratio among stroke and recurrent stroke than controls. However, this is more likely to protect rather than predispose to stroke.

CONCLUSION

The study demonstrates that the most frequent risk factor for stroke and recurrent stroke in the studied population is hypertension. It further showed that perhaps the presence of multiple risk factors is

permissive for the occurrence of stroke and recurrent stroke. The other identified risk factors were less frequently associated with stroke or recurrent stroke.

The limitation of our study is acknowledged especially with regard to the small sample size. However, it is a modest attempt at establishing the risk factors for stroke and recurrent stroke in our predominantly low income setting. Larger studies will further delineate the specific stroke risk factors prevalent in our community.

REFERENCES

1. Trinder P. Determination of Blood Glucose using 4-Aminophenazone as Oxygen Carrier Acceptor. *Journal of Clinical Pathology* 1969; 22: 246.
2. Searcy RL. Quantitative Determination of Triglycerides by Enzymatic End-point Colorimetric Method. Diagnostic Biochemistry 1961 McGraw HHill, New York.
3. Allain GC, Poon LS, Chan CS, et al. Quantitative Determination of Cholesterol using Enzymatic Colorimetric Method. *Clinical Chemistry* 1974; 20: 470-475.
4. Burstein M, Mortin R. Quantitative Determination of HDL Cholesterol using the Enzymatic Colorimetric Method. *Life Science* 1969; 8:345-347.
5. Friedewald WT, Levy RJ, Fredrickson DS. Estimation of the Concentration of LDL Cholesterol in Plasma without use of the Preparative Ultracentrifuge. *Clinical Chemistry* 1972; 18: 499-502.
6. Valery LF, Carlene ML, Derrick AB, Craig SA. Stroke Epidemiology: A Review of Population Based Studies of Incidence, Prevalence and Case Fatality in the 20th Century. *The Lancet* 2003; 2: 43-53.
7. Cabral NL, Goncalves AR, Longo AL, Eluf-Neto J. Incidence of Stroke Subtypes, Prognosis and Prevalence of Risk Factors in Joinville, Brazil: A Two-year Community-based Study. *Journal of Neurology, Neurosurgery and Psychiatry* 2009; 80 (7): 755-761.
8. Ogunrin AO. Recent Advances in the Management of Cerebrovascular Accident. Benin *Journal of Postgraduate Medicine* 2007; 9:28-40.
9. Osuntokun BO. Stroke in the Africans. *African Journal of Medical Sciences* 1977; 6 (2): 39-53.
10. Bonita R, Stewart AW, Beaglehole R. International Trends in Stroke Mortality 1970-1985. *Stroke* 1990; 32: 989-992.
11. Amu E, Ogunrin O, Danesi M. Reappraisal of Risk Factors for Stroke in Nigerian Africans - a Prospective Case-control Study. *African Journal of Neurological Sciences* 2005; 2:20-27.
12. Nwosu MC, Nwabueze A, Ikeh V. Stroke at the Prime of Life: a Study of Nigerian Africans between the ages of 16 and 45 years. *East African Medical Journal* 1992; 69: 384-390.
13. Mensah GA. Epidemiology of Stroke and High Blood Pressure in Africa. *Heart* 2008; 94: 697-705.
14. Ezzati M, Lopez AD, Rodgers A, et al, Lawes CM, Vandehoorn Law MR, et al. High Blood Pressure. ***In:*** Ezzati M, Lopez AD, Rodgers A, et al (Eds). Comparative Quantification of Health Risks: Global and Regional Burden of Diseases Attributable to Selected Risk Factors. Geneva: World Health Organisation 2004: 281-289.
15. Owolabi MO, Ugoya S, Platz T. Racial Disparity in Stroke Risk Factors: the Berlin-Ibadan Experience: a Retrospective Study. *Acta Neurologica Scandinavia* 2009; 119:81-87.
16. Osuntokun BO, Bademosi O, Akinkugbe OO, Oyediran AB, Carlisle R: Incidence of Stroke in an African City: Results from the Stroke Registry at Ibadan, Nigeria, 1973-1975. *Stroke* 1979; 10: 205-207.
17. Bwala SA. Stroke in a Sub-saharan Nigerian Hospital - a Retrospective Study. Tropical Doctor 1989; 19 910: 11-14.
18. Lopez AD, Mathers CD, Ezzati M, Vanderhoorn S, Lopez AD, et al. Comparative Quantification of Mortality and Burden of Disease Attributable to Selected Risk Factors. ***In:*** Lopez A. D, Mathers C. D, Ezzati M, et al (Eds.) Global Burden of Disease and Risk Factors. 2nd Edition. Washington D. C: World Bank 2006: 241-268.
19. Strauss E, Majumdar SR, Mcalister FA. New Evidence for Stroke Prevention: Scientific Review. *JAMA* 2002; 288:1388-1395.
20. Odusote A. Management of Stroke. *Nigerian Medical Practitioner* 1996; 32(5/6): 54-62.
21. Ogun SA, Ojini FI, Ogungbo B, Kolapo KO, Danesi M. Stroke in South-West Nigeria: a 10-year review. *Stroke* 2005; 36(6):112-122.
22. Ojini FI, Danesi MA. The Pattern of Neurological Admissions at the Lagos University Teaching Hospital. *Nigerian Journal of Clinical Practice* 2003; 5(1): 38-41.
23. Onwuchekwa AC, Onwuchekwa RC, Asekomeh EG. Stroke in Young Nigerian

Adults. *Journal of Vascular Nursing* 2009; 27(4): 98-102.
24. Lai SM, Alter M, Friday G, Sobel E. A Multifactorial Analysis of Risk Factors for Recurrence of Ischaemic Stroke. *Stroke* 1994; 25 (5):958-962.
25. Khan NI, Nazi L, Mushtaq S, Rukh L, Ali S, Hussain Z. Ischaemic Stroke: Prevalence of Modifiable Risk Factors in Male and Female Patients in Pakistan. *Pakistan Journal of Pharmaceutical Sciences* 2009; 22: 62-67.
26. Iso H, Jacobs DR, Wentworth D, et al, for the MRFIT Research Group. Serum Cholesterol Levels and Six-year Mortality from Stroke in 350,977 Men Screened for the Multiple Risk Factor Intervention Trial. *New England Journal of Medicine* 1989; 320:904-910.
27. American Heart Association (2001, December12). High Blood Triglycerides are Independent Risk Factors for Stroke. *Sciencedaily*. Retrieved May 28, 2011 from http://www.sciencedaily.com/releases/2001/12/01120163853.htm.
28. Ogunrin OA, Unuigbe E. Serum Lipids in Patients with Stroke: a Cross-sectional Case-control Study. Journal of National Medical Association 2008; 100: 9
29. Connor M, Rheeder P, Bryer A, Meredith M, Beukes M, et al. The South African Stroke Risk in General Practice Study. *The South African Medical Journal* 2005; 95:334-339.
30. Walker R. Stroke in Africa: Facing up to a Growing Problem. *Africa Health* 1997; 19(4): 28-30.